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Health and Environmental Effects Profile for 2-Methylaniline and 2-Methylanilin, Hydrochloride

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16. ABSTRACT

The Health and Environmental Effects Profile for 2-Methylaniline and 2-Methylaniline Hydrochloride was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 2-Methylaniline and 2-methylaniline hydrochloride have been evaluated as carcinogens. The human carcinogen potency factors (q_1^*) for 2-methylaniline and 2-methylaniline hydrochloride are 2.4×10^{-1} and 1.8×10^{-1} $(mg/kg/day)^{-1}$, respectively, for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 2-methylaniline and 2-methylaniline hydrochloride is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2-METHYLANILINE AND 2-METHYLANILINE HYDROCHLORIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

2-Methylaniline is a colorless to light yellow liquid at ambient temperature that turns reddish brown on exposure to light and air (Hawley, 1981; Verschueren, 1983). It is soluble in ethanol, diethyl ether and is slightly soluble in water (Hawley, 1981). 2-Methylaniline is a weak base, which forms salts with strong acids. 2-Methylaniline•HCl is a solid at ambient temperature. It is not soluble in benzene and diethyl ether, but is soluble in ethanol and water (IARC, 1982a; Weast, 1980). Chemically, 2-methylaniline•HCl will generally react similarly to 2-methylaniline. Because of its aqueous solubility, however, the environmental fate and transport of 2-methylaniline•HCl should be different from the parent compound.

As of January 1985, only two companies manufactured 2-methylaniline in the United States (SRI, 1985; USITC, 1985). The recent production volume of this chemical is not available, but one U.S. company manufactured between 1 and 10 million pounds in 1977 (U.S. EPA, 1977). 2-Methylaniline is commercially produced by iron reduction or catalytic hydrogenation of o-nitrotoluene (Sandridge and Staley, 1978). 2-Methylaniline•HCl was primarily manufactured by one company in the United States in 1977 (U.S. EPA, 1977). No recent information about its producers or production volume in the United States was available.

The principal commercial uses of 2-methylaniline and 2-methylaniline•HCl are in the manufacture of dye, rubber vulcanization accelerators, hypnotic and anesthetic pharmaceuticals, and pesticides (IARC, 1982a).

Data required to completely assess the environmental fate and transport of 2-methylaniline and 2-methylaniline•HCl could not be located in the available literature as cited in the Appendix. Photochemical reactions and chemical reactions with dissolved oxygen in the presence or absence of sunlight may be significant fate processes in natural water (Kondo, 1978; Meallier, 1969); however, because of insufficient data, the half-life of these reactions cannot be estimated. Experiments with both acclimated and unacclimated activated sludge indicate that the compound will biodegrade readily under conventional treatment conditions (Pitter, 1976; Kitano, 1978; Sasaki, 1978; Matsui et al., 1975). In the absence of available data, however, the significance of biodegradation in determining the fate of 2-methylaniline in natural water still remains unclear. From the available physical properties, it has been suggested that the loss of this compound from water through volatilization will not be significant. It has also been estimated that significant loss of the compound from water that has been adsorbed onto particulate matter is not likely. The formation of irreversible covalent bonds with humic materials in water causes some of the compound to be lost (Parris, 1980). Estimated BCFs (Lyman et al., 1982; Yoshida et al., 1983) show that 2-methylaniline will not bioconcentrate in aquatic organisms. The overall half-life of an unspecified isomer of methylaniline in a river water has been reported to be 1.0 days (Zoeteman et al., 1980).

The photochemical oxidation of 2-methylaniline in the presence of molecular oxygen in the atmosphere may be a significant fate process for this compound (Meallier, 1969). Based on the data for aniline (Atkinson, 1985), it is estimated that the oxidation reaction with atmospheric HO radical may be a significant loss process for this chemical. Based on its

physical properties and the estimation method of U.S. EPA (1980), it has been predicted that significant removal of 2-methylaniline through atmospheric physical processes will not occur.

Catalyzed oxidation by soil or clay may be one of the important reactions of 2-methylaniline in soil (Dragun and Helling, 1985). Alexander and Lustigman (1966) reported that a 1% suspension of Niagara silt loam soil completely degraded 2-methylaniline in 64 days.

The presence of both organic matter and crystalline mineral matter (Fe-oxides and phyllosilicates) in soil are important for the sorption of alkyl anilines in soil (Felice et al., 1982). At acidic pH, the amine will form salts that will ionize. Therefore, the ion-exchange capacity of soil may be an important factor in determining leachability from such soils. In basic soil, sorption onto organic matters or inorganic minerals may be important in determining the leachability (Felice et al., 1982). Based on its physical properties it has been predicted that volatilization from soil will not be a significant process; however, 2-methylaniline is likely to be transported from soil to surface water through rainwater washoffs.

Pertinent data regarding the fate and transport of 2-methylaniline•HCl could not be located in the available literature as cited in the Appendix. Predictions about its fate and transport are based on its physical properties and a few values estimated by Jaber et al. (1984). Because of its ionic nature, volatilization may not contribute significantly to the presence of 2-methylaniline•HCl in the atmosphere. 2-Methylaniline•HCl reaching the atmosphere as aerosol is likely to be removed much faster than the parent compound by both wet and dry deposition.

In water, 2-methylaniline·HCl will be present predominantly in the aquatic phase. In most cases, the chemical and biological fate of this compound will be similar to the parent compound because it will be effectively neutralized in large bodies of water. In case of large spills, however, the compound will persist longer. Based on the rate constant given by Jaber et al. (1984), the biodegradation of 2-methylaniline·HCl will not be significant in water. In soils, this compound is expected to follow similar patterns of environmental fate and transport as in water.

2-Methylaniline has been detected in surface waters, in effluents from wastewater treatment plants, in groundwaters near an underground coal gasification site and a coal tar waste disposal site, and in condensate and process retort water from oil-shale retort operations (Wegman and DeKorte, 1981; Neurath et al., 1977; Stuermer et al., 1982; Leenheer et al., 1982; Pereira et al., 1983; Dobson et al., 1985); a maximum concentration of 6 mg/ℓ was reported in process water from an oil-shale retorting process (Dobson et al., 1985). The maximum concentration of 2-methylaniline detected in any surface water was 1 µg/kg in water from River Alster, Germany (Neurath et al., 1977). The occurrence of 2-methylaniline in finished drinking water has not been reported. Therefore, it is unlikely that measurable amounts of this compound will be ingested through drinking water. No report on the presence of 2-methylaniline in ambient air could be found. Unspecified isomer(s) of methylaniline were found in fresh kale, celery and carrots. In fresh carrots, the concentration was as high as 7.2 mg/kg. Unspecified isomers of methylaniline have been detected in preserved shelled peas and red cabbage up to a concentration of 0.4 mg/kg. In preserved broken beans, 2-methylaniline was detected at a concentration of <0.1 mg/kg (Neurath et al., 1977). 2-Methylaniline was also detected in

black tea aroma (Vitzthum et al., 1975). Pertinent data regarding dermal exposure to methylaniline could not be located in the available literature as cited in the Appendix.

LC_{50} values of 117 and 26 mg/ℓ 2-methylaniline were reported for the golden orfe (Juhnke and Luedemann, 1978) and Daphnia magna. The blue-green alga, Microcystis aeruginosa, with a toxicity threshold of 0.31 mg/ℓ, was more sensitive than green alga, Scenedesmus quadricauda (6.3 mg/ℓ) or bacterium, Pseudomonas putida (16 mg/ℓ) (Bringmann and Kuehn, 1978, 1980). Pharmacokinetics studies with three marine molluscs and one fish species indicated that uptake of 2-methylaniline was rapid and steady-state was achieved in 4 hours; however, since elimination was also rapid, BCFs were <5 for all four species. Almost all radioactivity excreted by these species was in the form of the parent compound, indicating that they do not metabolize 2-methylaniline to a great extent (Knezovich and Crosby, 1985, 1986).

Pertinent data regarding the aquatic toxicity of 2-methylaniline•HCl could not be located in the available literature as cited in the Appendix.

2-Methylaniline is rapidly and extensively absorbed by the gastrointestinal tract of rats as indicated by the appearance of maximum blood levels of 2-methylaniline within 1 hour of oral dosing (Senczuk and Rucinska, 1984a) and the excretion of 95% of the radioactivity within 72 hours following oral dosing with ^{14}C-2-methylaniline (Cheever et al., 1980). 2-Methylaniline is also absorbed by the skin and the respiratory tract (Senczuk and Rucinska, 1984b; ACGIH, 1986).

Forty-eight hours after subcutaneous administration of ^{14}C-2-methylaniline•HCl in 0.9% saline, the highest concentration was found in the liver with 0.125 and 0.325% of the administered dose of radioactivity remaining after treatment with 50 or 400 mg/kg, respectively (Son et al.,

1980). Small amounts of radioactivity were also found in kidneys, lungs, spleen, colon and bladder. Ring hydroxylation with subsequent conjugation appears to be the primary metabolic pathway for 2-methylaniline in the rat (Cheever et al., 1980), although oxidation of the methyl or amino group also occurs to a limited extent (Son et al., 1980). Approximately 85, 92 and 95% of the administered radioactivity was present in the urine of rats within 12, 24 and 72 hours, respectively, of a 50 mg/kg gavage dose of 2-methylaniline•HCl in distilled water (Cheever et al., 1980). Rats treated subcutaneously with ^{14}C-2-methylaniline excreted 79, 3.3 and 1.4% of the dose in the urine, feces and expired air within 48 hours (Son et al., 1980).

2-Methylaniline•HCl was carcinogenic in both rats and mice (NCI, 1979; Weisburger et al., 1978; Hecht et al., 1982). The NCI (1979) reported increased incidences of multiple site sarcomas, subcutaneous fibromas and multiple site mesotheliomas in male rats; multiple site sarcomas, mammary fibroadenomas, splenic sarcomas and urinary bladder carcinomas or papillomas in female rats; multiple site hemangiosarcomas in male mice; and hepatocellular carcinomas or adenomas in female mice ingesting dietary 2-methylaniline•HCl. Weisburger et al. (1978) reported an increased incidence of tumors (NOS), subcutaneous fibromas/fibrosarcomas and urinary bladder transitional cell carcinomas in male rats and abdominal visceral hemangiomas/hemangiosarcomas in both male and female mice ingesting dietary 2-methylaniline•HCl. Hecht et al. (1982) reported an increased incidence of subcutaneous and splenic fibromas, peritoneal sarcomas and mammary gland fibroadenomas in male rats ingesting dietary 2-methylaniline•HCl. 2-Methylaniline has been the subject of an extensive number of mutagenicity tests including two international collaborative studies (Ashby, 1981; Ashby et al., 1985). Almost universally, negative results have been observed in

Salmonella with the notable exception in the case when hamster liver (rather than rat liver) was the source of exogenous metabolic activation. Positive results have been observed in a variety of mammalian *in vitro* systems capable of detecting gene mutations, single-strand DNA breaks, unscheduled DNA synthesis, sister-chromatid exchange, chromosome aberrations and morphological transformation. Based upon these findings, Ashby et al. (1985) concluded that 2-methylaniline is a general genotoxin that requires specific metabolic activation. No information on the developmental or reproductive effects of ingested or inhaled 2-methylaniline and 2-methylaniline•HCl were available. Meyers (1983) suggested, however, that 2-methylaniline may be teratogenic based on the similarity between the chemical structure and biological activity of 2-methylaniline and other known teratogens. Increased incidences of offspring of mice injected subcutaneously during gestation with 2-methylaniline have been reported in a Russian study (Golub et al., 1974). The noncarcinogenic effects of chronic ingestion of 2-methylaniline•HCl by rats included decreased lifespan at 3000 and 6000 ppm, decreased body weight gain at both doses and liver necrosis at the high dose in both males and females, myocardial fibrosis in males and urinary bladder hyperplasia in females at both doses (NCI, 1979). Rats receiving diets supplying 2-methylaniline at dosages of 15-24 mg/rat/day for 64 days followed by 7.5-12 mg/rat/day died by day 91 and had mucous membrane metaplasia and epithelial hyperplasia in the urinary bladder (Strombeck, 1946; Ekman and Strombeck, 1947). Similar bladder lesions occurred in rats maintained on diets containing 0.1% (1000 ppm) 2-methylaniline for up to 341 days (Ekman and Strombeck, 1949). Although not evaluated in any of the chronic studies with 2-methylaniline•HCl, increased methemoglobin levels occurred in rats, cats, mice, rabbits and dogs after short-term (1 day to

several weeks) exposure to 2-methylaniline (Short et al., 1983; McLean et al., 1969; Senczuk and Rucinska, 1984c; Smith et al., 1967; Goldstein et al., 1963).

Values for q_1*s of 2.4×10^{-1} $(mg/kg/day)^{-1}$ for 2-methylaniline and 1.8×10^{-1} $(mg/kg/day)^{-1}$ for 2-methylaniline•HCl were derived from the dose-response data for the increased incidence of skin fibromas in male rats in the study by Hecht et al. (1982). Water concentrations associated with increased lifetime risks at levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.5×10^{-3}, 1.5×10^{-4} and 1.5×10^{-5} mg/ℓ, respectively, for 2-methylaniline and 1.9×10^{-3}, 1.9×10^{-4} and 1.9×10^{-5} mg/ℓ, respectively, for 2-methylaniline•HCl, assuming that a 70 kg man consumes 2 ℓ water/day. F factors of 1.6 $(mg/kg/day)^{-1}$ for 2-methylaniline and 1.2 $(mg/kg/day)^{-1}$ for 2-methylaniline•HCl were also derived using the data from the Hecht et al. (1982) study. These chemicals are placed in Potency Group 2. Because the evidence for carcinogenicity in animals is sufficient, and inadequate in humans, both 2-methylaniline and 2-methylaniline hydrochloride are placed in IARC Group 2B (IARC, 1982b) and EPA Group B2 (U.S. EPA, 1986b). These chemicals, therefore, are probable human carcinogens and have a LOW hazard ranking under CERCLA.

An RQ of 1000 was derived for both chemicals based on myocardial fibrosis in male rats in the NCI (1979) study.

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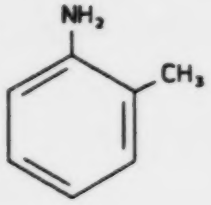
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
MED	Minimum effective dose
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutaminic oxaloacetic transaminase
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1.1.1. 2-Methylaniline. The chemical known as 2-methylaniline is also called 2-methylbenzenamine, o-toluidine, o-aminotoluene, o-methylaniline, o-methylbenzenamine, o-tolylamine, 2-aminotoluene and 2-toluidine (SANSS, 1986). The structure, empirical formula, molecular weight and CAS Registry number for this chemical are as follows:



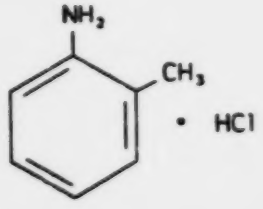
2-methylaniline

Molecular weight: 107.15

Empirical formula: C_7H_9N

CAS Registry number: 95-53-4

1.1.2. 2-Methylaniline•HCl. Some of the common synonyms for 2-methylaniline•HCl are benzenamine, 2-methyl-, hydrochloride; o-toluidine hydrochloride; 1-amino-2-methylbenzene hydrochloride; 2-aminotoluene hydrochloride; o-aminotoluene hydrochloride; o-tolylamine hydrochloride (IARC, 1982a). The structure, empirical formula, molecular weight and CAS Registry number for this chemical are as follows:



2-methylaniline • HCl

Molecular weight: 143.62

Empirical formula: $C_7H_{10}NCl$

CAS Registry number: 636-21-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1.2.1. 2-Methylaniline. 2-Methylaniline is a colorless to light yellow liquid at ambient temperature that turns reddish brown on exposure to light and air (Hawley, 1981; Verschueren, 1983). It is volatile with steam. 2-Methylaniline is soluble in ethanol and ethyl ether and is slightly soluble in water (Hawley, 1981). Some of the physical properties of this compound are given below:

Melting point:	-24.4°C (α-form)	Verschueren, 1983
	-16.0°C (β-form)	Verschueren, 1983
Boiling point:	200°C	Verschueren, 1983
Specific gravity:	1.004 at 20/4°C	Verschueren, 1983
Flash point:	85°C	Hawley, 1981
Vapor pressure (mm Hg):		
at 20°C	0.1	Verschueren, 1983
at 25°C	0.32	Yoshida et al., 1983
at 30°C	0.3	Perry and Green, 1984
at 44°C	1	Verschueren, 1983
Water solubility (mg/ℓ):		
at 25°C	15,000	Verschueren, 1983
at 25°C	16,000	Huyskens et al., 1975
Henry's Law Constant :	3.0×10^{-6} atmos-m^3 mol^{-1} (estimated)	Verschueren, 1983
Log K_{ow}:	1.32 (recommended)	Hansch and Leo, 1985
Log K_{oc}:	2.10	Yoshida et al., 1983
Air odor threshold:	0.25 ppm	Amoore and Hautala, 1983
Water odor threshold:	11 mg/ℓ	Amoore and Hautala, 1983

pKa:		
at 20°C	4.54	Perrin, 1972
at 25°C	4.45	Perrin, 1972
at 25°C	4.44	Huyskens et al., 1975
Conversion factor:	1 ppm = 4.38 mg/m³	

Chemically, 2-methylaniline will act as a weak base and is expected to participate in reactions involving the amino group. One of the important reactions is diazotization, which is used in the manufacture of dyes. Reactions of 2-methylaniline that are environmentally significant are discussed in Chapter 2.

1.2.2. 2-Methylaniline•HCl. 2-Methylaniline•HCl is a solid at ambient temperature. It is not soluble in benzene and diethyl ether, but is soluble in ethanol and water (IARC, 1982a; Weast, 1980). Some of the available physical properties of this compound are given below:

Melting point:	215°C	Weast, 1980
Boiling point:	242°C	Weast, 1980
Water solubility:	soluble in water	IARC, 1982a

Chemically, 2-methylaniline•HCl will react similarly to 2-methylaniline; however, because of its aqueous solubility, the environmental fate of the hydrochloride will be different from the parent compound. Details of the environmental behavior of 2-methylaniline•HCl are discussed in Chapter 2.

1.3. PRODUCTION DATA

1.3.1. 2-Methylaniline. According to the U.S. EPA TSCA production file (U.S. EPA, 1977), there were two manufacturers and one importer of this chemical in the United States in 1977. As of January 1985, two companies, DuPont Co., Inc., Deepwater, NJ, and First Mississippi Corp., Pascagoula, MS, manufactured this chemical in the United States (SRI, 1985; USITC, 1985).

Although the recent production volume of this chemical is not available, First Mississippi Corp. produced between 1 and 10 million pounds in 1977; the production volume of this chemical from DuPont Co. in 1977 was not reported (U.S. EPA, 1977). Approximately 3 million pounds of 2-methylaniline was imported in the United States in 1979 (IARC, 1982a). 2-Methylaniline is commercially produced by iron reduction or catalytic hydrogenation of o-nitrotoluene (Sandridge and Staley, 1978).

1.3.2. 2-Methylaniline•HCl. According to the U.S. EPA TSCA production file (U.S. EPA, 1977), Drake Chemicals, Inc., Lock Haven, PA, manufactured 2-methylaniline•HCl in the United States in 1977; Kodak Co., Rochester, NY, produced <1000 pounds of this chemical during the same year. American Cyanamid Co., Bound Brook, NJ, imported unspecified amounts of 2-methylaniline•HCl in the United States in 1977 (U.S. EPA, 1977). No information about recent U.S. producers of this chemical or its present or past U.S. production volumes was available.

1.4. USE DATA

The principal commercial uses of 2-methylaniline and 2-methylaniline•HCl are in the manufacture of dyes, rubber vulcanization accelerators, hypnotic and anesthetic pharmaceuticals, and the pesticide siduron (IARC, 1982a).

1.5. SUMMARY

2-Methylaniline is a colorless to light yellow liquid at ambient temperature that turns reddish brown on exposure to light and air (Hawley, 1981; Verschueren, 1983). It is soluble in ethanol and diethyl ether and is slightly soluble in water (Hawley, 1981). 2-Methylaniline is a weak base, which forms salts with strong acids. 2-Methylaniline•HCl is a solid at ambient temperature. It is not soluble in benzene and diethyl ether, but is

soluble in ethanol and water (IARC, 1982a; Weast, 1980). Chemically, 2-methylaniline•HCl will generally react similarly to 2-methylaniline. Because of its aqueous solubility, however, the environmental fate and transport of 2-methylaniline•HCl should be different from the parent compound.

As of January 1985, only two companies manufactured 2-methylaniline in the United States (SRI, 1985; USITC, 1985). The recent production volume of this chemical is not available, but one U.S. company manufactured between 1 and 10 million pounds in 1977 (U.S. EPA, 1977). 2-Methylaniline is commercially produced by iron reduction or catalytic hydrogenation of o-nitrotoluene (Sandridge and Staley, 1978). 2-Methylaniline•HCl was primarily manufactured by one company in the United States in 1977 (U.S. EPA, 1977). No recent information about its producers or production volume in the United States was available.

The principal commercial uses of 2-methylaniline and 2-methylaniline•HCl are in the manufacture of dye, rubber vulcanization accelerators, hypnotic and anesthetic pharmaceuticals, and pesticides (IARC, 1982a).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. 2-Methylaniline. Since 2-methylaniline changes color when exposed to light and air (see Section 1.2.1.), it is likely that both photochemical and chemical reactions with dissolved oxygen in the presence or absence of sunlight may be significant in natural waters; however, data regarding these reactions could not be located in the available literature. Kondo (1978) studied the photodegradation of 3-methylaniline irradiated with a fluorochemical lamp (maximum wavelength 350 nm; range 300-400 nm) and reported a half-life of 2.8 days. This study suggests that a similar photochemical reaction is possible for 2-methylaniline. Similarly, the gas phase reaction of 2-methylaniline in the presence of molecular oxygen with light of maximum wavelength 365 nm (Meallier, 1969) suggests that a similar oxidation reaction is possible in water.

The biodegradation of 2-methylaniline in water has been studied by several investigators. Several species of pure microbial cultures including bacteria, Pseudomonas sp., Bacillus sp. (Udod, 1973; Walker and Harris, 1969), R. rhodochrous sp. (Appel et al., 1984) and fungus, Goetrichum candidum (Bordeleau and Bartha, 1972), are capable of biodegrading 2-methylaniline. 2-Methylaniline, however, failed to act as a sole carbon source for other species of pure bacterial culture of the genus Micrococcus, Vibrio and Achromobacter (Kramer and Doetsch, 1950). Although biodegradation studies with pure cultures are generally important for establishing degradation pathways, they normally do not apply to biodegradation under field conditions where mixed cultures are present.

The biodegradation of 2-methylaniline with mixed microorganisms has been reported by several authors. With aniline or 2-methylaniline acclimated

activated sludge, 2-methylaniline has been shown to biodegrade readily (Thom and Agg, 1975). For example, 2-methylaniline-acclimated activated sludge almost completely biodegraded 2-methylaniline in 4-5 days (Pitter and Richtrova, 1974; Pitter, 1976). With aniline-acclimated activated sludge, Malaney (1960) reported >50% degradation of 2-methylaniline present at an initial concentration of 500 mg/ℓ in 8 days.

2-Methylaniline can also be biodegraded by activated sludge without prior acclimatization. With sewage seed as microbial inoculum and the standard dilution as the method of incubation, an oxidation equivalent to 50% of the BODT occurred in 5 days with 2-methylaniline at an initial concentration of 1.25-2.5 ppm (Heukelkian and Rand, 1955). Heukelkian and Rand (1955) reported <10% oxidation of an unspecified initial concentration of 2-methylaniline under similar experimental conditions. Under OECD test conditions, which consist of incubating a test compound at a concentration equivalent to 20 mg/ℓ DOC in standard shake flasks with concentrated treated sewage effluent or activated sludge as microbial inoculum for up to 28 days, showed that this compound generally biodegraded >80% in 7 days (Brown and Laboureur, 1983). With an initial test substance concentration of 100 mg/ℓ and activated sludge as microbial inoculum, >60% degradation of 2-methylaniline was reported in 2 weeks at 25°C (Kitano, 1978). Other investigators have also confirmed the easy biodegradability of 2-methylaniline with activated sludge as microbial inoculum (Sasaki, 1978; Matsui et al., 1975). On the other hand, with activated sludge from two municipal plants and a small aerobic digestion unit as microbial inoculum, Marion and Malaney (1964) reported no oxidation of 2-methylaniline and that the compound was slightly toxic to one sludge.

It can be concluded from the previous discussion that 2-methylaniline may biodegrade in water with or without acclimated microorganisms; however, these data did not reflect the conditions that may be encountered in environmental waters. In the absence of adequate field data for estimating the value for the rate constant for biodegradation, it is difficult to estimate the biodegradation half-life of 2-methylaniline in ambient water.

The rate of volatilization of 2-methylaniline from water is unknown. Based on the estimated value for Henry's Law constant (see Section 1.2.1.) for this compound and the volatility characteristics associated with various ranges of this constant (Lyman et al., 1982), significant volatilization of the compound from water is unlikely. The rate of removal of this compound from the aquatic phase by sorption onto suspended particles in water may be estimated from the K_{oc}. Since the estimated log K_{oc} for this compound is 2.10 (see Section 1.2.), significant sorption of this compound is not likely; however, it is likely to form covalently bonded compounds with the carbonyl groups of the humic substances present in aquatic suspended matters, although this binding is weakest for the ortho substituent of the aromatic amines (Parris, 1980). This irreversible covalent bonding may remove some of the aquatic 2-methylaniline to the sediment.

No experimental value for the BCF of 2-methylaniline in aquatic organisms could be located in the available literature. The BCF value can be estimated from the equation log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982). Substituting a value of 1.32 for log K_{ow}, the BCF is estimated as 5.9. Using a different regression equation, Yoshida et al. (1983) estimated a BCF value of 0.5. Both these values indicate that 2-methylaniline will not bioconcentrate in aquatic organisms.

2.1.2. 2-Methylaniline•HCl. Adequate information regarding the fate and transport of 2-methylaniline•HCl in environmental media could not be located in the available literature; however, based on its physical properties and a few estimated characteristics of this compound, predictions about some of its environmental fate and transport processes have been made.

In water, the volatilization of this compound to the atmosphere and sorption onto suspended particulate matter will be even less than the parent compound because of its higher aqueous solubility. 2-Methylaniline•HCl will be present predominantly in the aquatic phase. In water, addition of small amounts of 2-methylaniline•HCl will not change the pH of the water, and the compound will be effectively neutralized and its fate will be similar to the parent compound; when large amounts are added, the removal of the compound through oxidation will be much slower (Jaber et al., 1984), and the compound will persist in water. Jaber et al. (1984) reported the biodegradation rate constant for 2-methylaniline•HCl as 1×10^{-10} mℓ $cell^{-1}$ $hour^{-1}$ (Jaber et al., 1984), although the basis of the estimated value is not clear. Based on this biodegradation rate constant and assuming a concentration of microorganisms in surface water of 10^6 cell $mℓ^{-1}$ (Oduntan and Odeyemi, 1984), the half-life of biodegradation can be estimated to be ~290 days. Therefore, it is not expected to be a significant process in determining the fate of 2-methylaniline•HCl in water.

2.2. AIR

2.2.1. 2-Methylaniline. Adequate information regarding the fate of 2-methylaniline and its hydrochloride in the atmosphere was not available. In the presence of molecular oxygen, 2-methylaniline will undergo photochemical oxidation in the troposphere (Meallier, 1969). At oxygen pressures <200 mm Hg, the reaction was first-order and the photochemical oxidizability

was shown to be in the order 4-methyl>2-methyl>3-methyl. The half-life of 2-methylaniline that results from this reaction cannot be estimated, however, because the rate constant for the reaction was not reported. Another atmospheric reaction that may be significant in determining the fate of 2-methylaniline is its reaction with HO radical. Although the rate constant for HO radical reaction with 2-methylaniline was not available, the rate constant for the aniline reaction at 25°C is given as 118×10^{-12} cm^3 $molecule^{-1}$ sec^{-1} (Atkinson, 1985). Based on an atmospheric HO radical concentration of 10^6 molecule cm^{-3} (U.S. EPA, 1980), the half-life for HO radical reaction with 2-methylaniline is estimated as <2 hours. Therefore, the atmospheric HO radical reaction with 2-methylaniline is expected to be significant.

Data regarding the rate of removal of atmospheric 2-methylaniline through physical removal mechanisms could not be located in the available literature. Based on the conclusion reached by U.S. EPA (1980) that adsorption of atmospheric chemicals will be a reasonable vapor-phase removal mechanism only for chemicals with saturation vapor pressure of $\leq 10^{-7}$ torr, it is predicted that significant amounts of 2-methylaniline (vapor pressure, 0.1 mm Hg at 20°C) will not be removed through adsorption onto atmospheric aerosol particles. Because of its significant water solubility the removal of atmospheric 2-methylaniline through dissolution into raindrops and subsequent precipitation seems likely.

2.2.2. 2-Methylaniline•HCl. Volatilization losses of 2-methylaniline•HCl to the atmosphere are not likely since the vapor pressure of this ionic compound is expected to be much lower than the parent compound. 2-Methylaniline•HCl that reaches the atmosphere as aerosol is likely to be removed much faster than 2-methylaniline; this is attributed to both wet and

dry deposition. The removal of atmospheric 2-methylaniline•HCl by oxidation with HO radical or RO_2 radical will be much slower than the parent compound (Jaber et al., 1984).

2.3. SOIL

2.3.1. 2-Methylaniline. According to Dragun and Helling (1985), 2-methylaniline will undergo soil- or clay-catalyzed oxidation. Although the half-life of this reaction cannot be estimated because the rate constant is unknown, the reaction may be significant in determining the fate of 2-methylaniline in soil. The biodegradation potential of 2-methylaniline in soils has been studied by a few investigators. Bordeleau and Bartha (1972) isolated a peroxidase from the soil fungus, G. candidum that was shown to convert 2-methylaniline to its azo-product. Medvedev and Davydov (1972) found that microbial transformation of 2-methylaniline in soils left very stable decomposition products, which did not degrade even after 3 months. Alexander and Lustigman (1966) reported that a 1% suspension of Niagara silt loam soil completely degraded 2-methylaniline in 64 days, although the biodegradation of the 2-isomer was much slower than the 3- or 4-isomer.

Felice et al. (1982) studied the soil sorption of alkyl anilines and determined that the presence of both organic matter and crystalline mineral matter (Fe-oxides and phyllosilicates) in the soil were important for the sorption of alkyl anilines in soil. The soil pH is also important in determining the leachability of alkyl anilines from soils. At acidic pH, the amine will form salts that will ionize. Therefore, the ion-exchange capacity of soil may be an important factor in determining leachability from acidic soils. In basic soils, the sorption onto organic matters or inorganic minerals may play an important role in determining the leachability of 2-methylaniline from soil.

Based on its volatility characteristics from water (see Section 2.1.), the transport of 2-methylaniline from soil to the atmosphere through volatilization may not be an important process. The reasonable water solubility, however, indicates that 2-methylaniline may be transported from soil to surface water through rainwater washoffs.

2.3.2. 2-Methylaniline·HCl. In soils, the fate and transport of the 2-methylaniline·HCl is expected to be similar to that in water. The overall half-life of an unspecified isomer of methylaniline in river water has been reported to be 1 day (Zoeteman et al., 1980).

2.4. SUMMARY

Data required to completely assess the environmental fate and transport of 2-methylaniline and 2-methylaniline·HCl could not be located in the available literature. Photochemical reactions and chemical reactions with dissolved oxygen in the presence or absence of sunlight may be significant fate processes in natural water (Kondo, 1978; Meallier, 1969); however, because of insufficient data, the half-life of these reactions cannot be estimated. Experiments with both acclimated and unacclimated activated sludge, indicate that the compound will biodegrade readily under conventional treatment conditions (Pitter, 1976; Kitano, 1978; Sasaki, 1978; Matsui et al., 1975). In the absence of available data, however, the significance of biodegradation in determining the fate of 2-methylaniline in natural water still remains unclear. From the available physical properties, it has been suggested that the loss of this compound from water through volatilization will not be significant. It has also been estimated that significant loss of the compound from water, which is due to sorption onto particulate matter, is not likely. Some of the compound will be lost from water because of the formation of irreversible covalent bonds with

humic materials in water (Parris, 1980). Estimated BCFs (Lyman et al., 1982; Yoshida et al., 1983) show that the compound will not bioconcentrate in aquatic organisms. The overall half-life of an unspecified isomer of methylaniline in a river water has been reported to be 1.0 days (Zoeteman et al., 1980).

The photochemical oxidation of 2-methylaniline in the presence of molecular oxygen in the atmosphere may be a significant fate process for this compound (Meallier, 1969). Based on the data for aniline (Atkinson, 1985), it is estimated that the oxidation reaction with atmospheric HO radical may be a significant loss process for this chemical. Based on its physical properties and the estimation method of U.S. EPA (1980), it has been predicted that significant removal of 2-methylaniline through atmospheric physical processes will not occur.

Catalyzed oxidation by soil or clay may be one of the important reactions of 2-methylaniline in soil (Dragun and Helling, 1985). Alexander and Lustigman (1966) reported that a 1% suspension of Niagara silt loam soil completely degraded 2-methylaniline in 64 days.

The presence of both organic matter and crystalline mineral matter (Fe-oxides and phyllosilicates) in soil are important for the sorption of alkyl anilines in soil (Felice et al., 1982). At acidic pH, the amine will form salts that will ionize. Therefore, the ion-exchange capacity of soil may be an important factor in determining leachability from such soils. In basic soil, sorption onto organic matters or inorganic minerals may be important in determining the leachability (Felice et al., 1982). Based on its physical properties it has been predicted that volatilization from soil will not be a significant process; however, 2-methylaniline is likely to be transported from soil to surface water through rainwater washoffs.

Pertinent data regarding the fate and transport of 2-methylaniline•HCl could not be located in the available literature. Predictions about its fate and transport are based on its physical properties and a few values estimated by Jaber et al. (1984). Because of its ionic nature, volatilization may not contribute significantly to the presence of 2-methylaniline•HCl in the atmosphere. 2-Methylaniline•HCl reaching the atmosphere as aerosol is likely to be removed much faster than the parent compound by both wet and dry deposition.

In water, 2-methyaniline•HCl will be present predominantly in the aquatic phase. In most cases, the chemical and biological fate of this compound will be similar to the parent compound because it will be effectively neutralized in large bodies of water. In case of large spills, however, the compound will persist longer. Based on the rate constant given by Jaber et al. (1984), the biodegradation of 2-methylaniline•HCl will not be significant in water. In soils, this compound is expected to follow similar patterns of environmental fate and transport as in water.

3. EXPOSURE

3.1. WATER

2-Methylaniline has been found in a few surface waters, in secondary effluents from wastewater treatment plants, in groundwater near an underground coal gasification site, and in condensate and process retort water from oil-shale retort operations. For example, Ellis et al. (1982) qualitatively detected 2-methylaniline in secondary effluent samples from a publicly-owned treatment works in Illinois. Similarly, Meijers and Van der Leer (1976) detected 2-methylaniline in river water from the Netherlands at a maximum average quarterly concentration of 1.3 ppb (µg/ℓ). The reported concentrations of 2-methylaniline in a few surface waters, groundwater and retort water from in situ oil-shale retort operations are shown in Table 3-1. Unidentified methylaniline isomers were found in the effluents from a few chemical manufacturing operations in Kingsport and Morristown, TN (U.S. EPA, 1976). Trace amounts of 2-methylaniline were found in the water from the North Sea, probably because of ocean dumping of chemical wastes (Greve, 1971), and in upper Catawba River, NC, probably because of dye manufacturing in the area (U.S. EPA, 1976). 2-Methylaniline was found in the effluent from coking works (U.S. EPA, 1976). 2-Methylaniline at a concentration of 9800 µg/kg was detected in Niagara River sediments at a depth of 9 feet (U.S. EPA, 1986a). It was also qualitatively detected in groundwater near a coal tar waste disposal site in St. Louis Park, MN (Pereira et al., 1983).

TABLE 3-1

Concentrations of 2-Methylaniline in Aquatic Samples

Type of Sample	Source of Sample	Concentration (ppb)	Reference
Surface water	River Rhine at Lobith	0.03(6)[a]	Wegman and DeKorte, 1981
Surface water	tributary of Rhine (Boven Merwede)	0.07(8)[a]	Wegman and DeKorte, 1981
Surface water	tributary of Rhine (Ijessel)	0.20(8)[a]	Wegman and DeKorte, 1981
Surface water	River Alster, Germany	~1[b]	Neurath et al., 1977
Surface water	River Au near Hetlingen, Germany	0.5[b]	Neurath et al., 1977
Surface water	River Pinnau, Germany	0.3[b]	Neurath et al., 1977
Groundwater	wells from Hoe Creek in Wyoming 15 months after completion of underground coal gasification	0.06-9.2[c]	Stuermer et al., 1982
Wastewater	process retort water from in situ oil-shale retorting process at Logan, WA	3.4×10^3	Leenheer et al., 1982
Wastewater	condensate retort water from in situ oil-shale retorting process at Logan, WA	0.2×10^3	Leenheer et al., 1982
Wastewater	process water from retorting oil-shale	6×10^3	Dobson et al., 1985

[a]Values in parentheses are percent occurrence.

[b]Values are in µg/kg and may be slightly different from the given ppb values.

[c]The o- and p-isomers were not separated.

The occurrence of 2-methylaniline in finished drinking water has not been reported. However, this compound is not generally measured in routine drinking water tests. Moreover, only a few areas where dyes are manufactured and used may have 2-methylaniline in drinking water. Therefore, comprehensive drinking water studies may have missed the occurrence of this compound.

3.2. AIR

Although 2-methylaniline at a quantity of 61 ng/cigarette was reported in mainstream tobacco smoke (Patrianakos and Hoffman, 1979) and unspecified isomers of methylaniline were detected in smoke particulates from the smoldering of polyurethane foam in air (Kuriakose and Browner, 1980), no report of its presence in ambient air could be found. In an occupational survey by NIOSH of two coal liquefaction pilot facilities, the concentrations of aromatic amines in air were found to be below the OSHA standards (Harris et al., 1980).

3.3. FOOD

Unidentified isomers of methylaniline were found at concentrations of 1.1 mg/kg in fresh kale and celery and 7.2 mg/kg in fresh carrots. In preserved vegetables, unspecified methylaniline isomers at concentration levels of 0.4 and 0.2 mg/kg were reported in shelled peas and red cabbage, respectively. In addition, preserved broken beans were found to contain <0.1 mg/kg of 2-methylaniline (Neurath et al., 1977). Vitzthum et al. (1975) identified 2-methylaniline in the volatile constituents of black tea aroma. With these limited data it is not possible to estimate the human exposure to 2-methylaniline through the consumption of foods.

3.4. DERMAL

Pertinent data regarding the level of dermal exposure to 2-methylaniline could not be located in the available literature as cited in the Appendix.

3.5. SUMMARY

2-Methylaniline has been detected in surface waters, in effluents from wastewater treatment plants, in groundwaters near an underground coal gasification site, and a coal tar waste disposal site, and in condensate and process retort water from oil-shale retort operations (Wegman and DeKorte, 1981; Neurath et al., 1977; Stuermer et al., 1982; Leenheer et al., 1982; Pereira et al., 1983; Dobson et al., 1985); a maximum concentration of 6 mg/ℓ was reported in process water from an oil-shale retorting process (Dobson et al., 1985). The maximum concentration of 2-methylaniline detected in any surface water was 1 µg/kg in water from River Alster, Germany (Neurath et al., 1977). The occurrence of 2-methylaniline in finished drinking water has not been reported. Therefore, it is unlikely that measurable amounts of this compound will be ingested through drinking water. No report on the presence of 2-methylaniline in ambient air could be found. Unspecified isomers of methylaniline were found in fresh kale, celery and carrots. In fresh carrots, the concentration was as high as 7.2 mg/kg. Unspecified isomers of methylaniline have been detected in preserved shelled peas and red cabbage up to a concentration of 0.4 mg/kg. In preserved broken beans, 2-methylaniline was detected at a concentration of <0.1 mg/kg (Neurath et al., 1977). 2-Methylaniline was also detected in black tea aroma (Vitzthum et al., 1975). Pertinent data regarding dermal exposure to methylaniline could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

After gavage administration of 50 mg/kg of 2-[methyl-^{14}C]aniline•HCl (>99% pure) in distilled water to male Sprague-Dawley rats, ~92 and 95% of the administered radioactivity was found in the urine within 24 and 72 hours, respectively (Cheever et al., 1980). Senczuk and Rucinska (1984a) reported that blood levels of 2-methylaniline increased proportionately to the doses in rats treated by gavage with 2-methylaniline. The maximum levels were reached 1 hour after dosing. Additional details were not provided in the abstract.

Dermal absorption was also studied by Senczuk and Rucinska (1984b). After dermal exposure of rats to 0.25-0.75% aqueous solutions of 2-methylaniline for 2-6 hours, the blood levels of 2-methylaniline rose in a dose-related and duration-related manner. Additional details were not provided in the abstract. 2-Methylaniline is also absorbed by the respiratory tract (ACGIH, 1986).

4.2. DISTRIBUTION

Son et al. (1980) gave groups of two male F344 rats a single subcutaneous injection of 50 or 400 mg/kg 2-[methyl-^{14}C]aniline•HCl in 0.9% saline. All rats were killed 48 hours after administration, and their livers, kidneys, lungs, spleens, colons and bladders were assayed for radioactivity. In rats given 50 mg/kg, the above organs contained the following average percentages of administered radioactivity, respectively: 0.125, 0.016, 0.0035, 0.002, not done and 0.00035%. In rats given 400 mg/kg, these organs contained 0.325, 0.055, 0.015, 0.04, 0.005 and 0.015% of the administered radioactivity, respectively.

4.3. METABOLISM

Ring hydroxylation with subsequent conjugation is the primary metabolic pathway of 2-methylaniline in the rat (Cheever et al., 1980). In rats treated by gavage with 50 mg/kg 2-[methyl-^{14}C]aniline•HCl in distilled water, ~37% of the dose was identified as unchanged 2-methylaniline and ~52% was identified as 4-amino-3-methylphenol conjugates in the urine collected for 72 hours after dosing. Similarly, when 500 mg/kg of unlabeled 2-methylaniline in corn oil was administered to rats by gavage, unchanged 2-methylaniline and conjugates of aminomethylphenols were identified in the urine (Cheever et al., 1980).

Groups of two male F344 rats were treated with a single subcutaneous injection of either 50 or 400 mg/kg of 2-[methyl-^{14}C]aniline•HCl as a suspension in 1.5-2.0 mL of a 0.9% saline solution (Son et al., 1980). The metabolites identified in the urine collected within 24 hours of dosing are listed in Table 4-1 and the proposed pathway is illustrated in Figure 4-1. Ring hydroxylation represented ~44% of the administered 2-methylaniline (42% in the para-position as indicated by pathway IIIA, 2% in the ortho-position as indicated by pathway IIIB); oxidation of the methyl group (pathway I) represented ~2% of the administered dose; and oxidation of the amino group (pathway IV) also occurs to a limited extent. 2-Methylaniline can be acetylated directly (pathway II) or subsequent to hydroxylation or oxidation. Acetylated compounds accounted for 23% of the total identified urinary metabolites. Sulfate and glucuronate conjugates accounted for 66 and 11%, respectively, of the total identified urinary metabolites. Approximately 1% of the dose was excreted in the expired air as $^{14}CO_2$. The authors stated that preliminary data indicated that there are wide differences among guinea pigs, rats and hamsters in the relative extent of the different conjugation reactions, but they provided no further details.

TABLE 4-1

Metabolites Present in the Urine of Male Rats Within 24 Hours After a Subcutaneous Injection of 400 mg/kg 2-[Methyl-^{14}C]aniline*

Metabolites	% Dose
Acid-conjugated metabolites	
4-Amino-cresyl sulfate	27.8
N-Acetyl-4-amino-m-cresyl sulfate	8.5
2-Amino-m-cresyl sulfate	2.1
4-Amino-m-cresyl glucuronide	2.6
N-Acetyl-4-amino-m-cresyl glucuronide	2.8
N-Acetyl-o-aminobenzyl glucuronide	1.3
Unidentified conjugated metabolites	5.9
TOTAL	51.0
Ether-extractable metabolites	
2-Methylaniline	5.1
Azoxytoluene	0.2
o-Nitrosotoluene	$\leq$0.1
N-Acetyl-o-toluidine	0.2
N-Acetyl-o-aminobenzyl alcohol	0.3
4-Amino-m-cresol	0.06
N-Acetyl-4-amino-m-cresol	0.3
Anthranilic acid	0.3
N-Acetylanthranilic acid	0.3
TOTAL	$\leq$6.9

*Source: Son et al., 1980

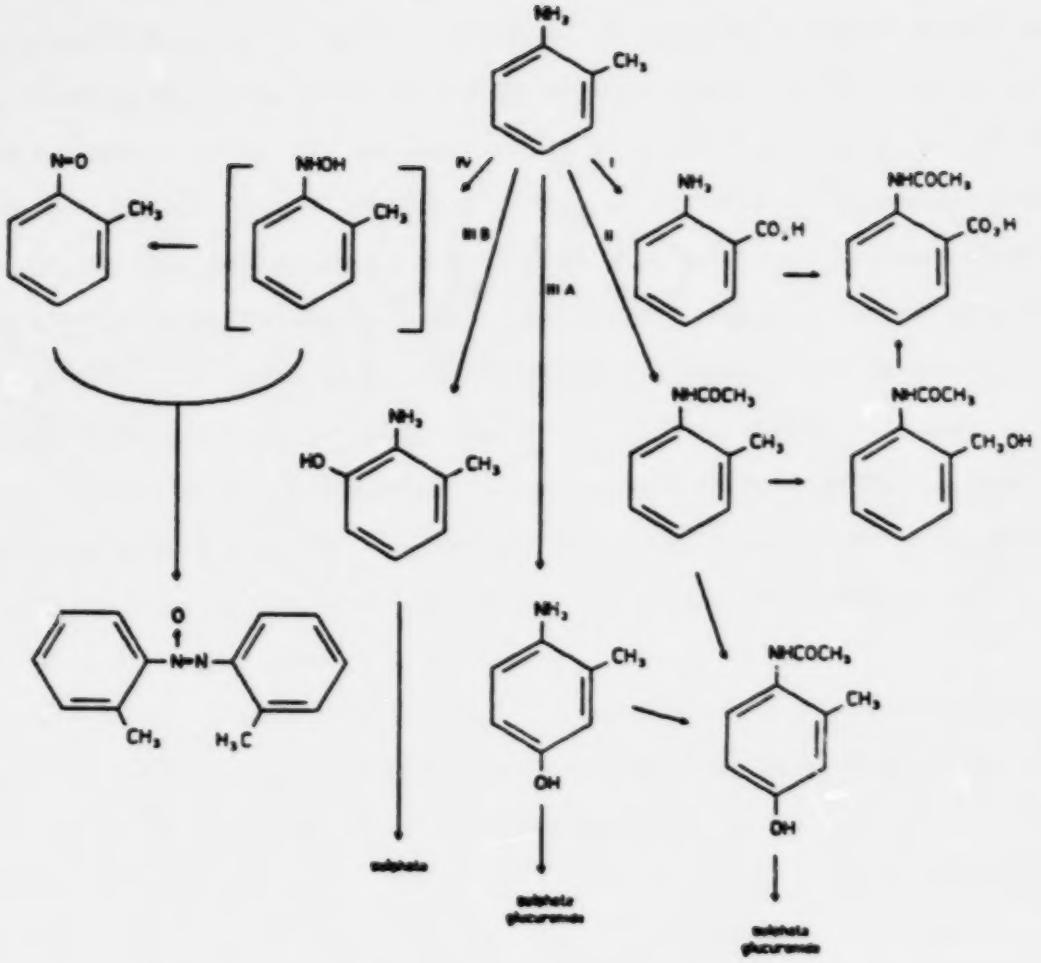


FIGURE 4-1

Metabolism of 2-[Methyl-^{14}C]aniline (Brackets indicate a metabolite not actually identified but for which indirect evidence exists)

Source: Son et al., 1980

4.4. EXCRETION

The primary route of excretion of 2-methylaniline in the rat is urinary (Cheever et al., 1980; Son et al., 1980). Approximately 92 and 95% of the radioactivity in a 50 mg/kg oral dose of 2-[methyl-^{14}C]aniline•HCl was excreted in the urine after 24 and 72 hours, respectively (Cheever et al., 1980). Approximately 85% had been excreted in the first 12 hours. Of the excreted radioactivity, 37.4 and 51.7% was in the form of unchanged 2-methylaniline and 4-amino-3-methylphenol conjugates, respectively. Oral administration of 500 mg/kg doses of unlabeled 2-methylaniline in corn oil to rats resulted in the appearance of 21% of the 2-methylaniline (unchanged) in the urine after 24 hours (Cheever et al., 1980). Attempts to quantitate other urinary metabolites (conjugates of aminomethylphenols) failed because of decomposition problems. Senczuk et al. (1984) reported that 26% of the 2-methylaniline administered intragastrically to rats was excreted unchanged in the urine within 24 hours of dosing.

Son et al. (1980) reported that 24 hours after a single subcutaneous dose of 400 mg/kg 2-[methyl-^{14}C]aniline•HCl in male F344 rats, an average of 56, 2.3 and 1% of the dose appeared in the urine, feces and expired air, respectively. After 48 hours, an average of 79, 3.3 and 1.4% of the dose appeared in the urine, feces and expired air, respectively. Ether-extractable urinary metabolites accounted for 7.2% of the dose, and acid-conjugated urinary metabolites accounted for 51% of the dose.

4.5. SUMMARY

2-Methylaniline is rapidly and extensively absorbed by the gastrointestinal tract of rats as indicated by the appearance of maximum blood levels of 2-methylaniline within 1 hour of oral dosing (Senczuk and Rucinska, 1984a) and the excretion of 95% of the radioactivity within 72 hours following oral dosing with ^{14}C-2-methylaniline (Cheever et al., 1980).

2-Methylaniline is also absorbed by the skin and the respiratory tract (Senczuk and Rucinska, 1984b; ACGIH, 1986).

Forty-eight hours after subcutaneous administration of ^{14}C-2-methylaniline•HCl in 0.9% saline, the highest concentration was found in the liver with 0.125 and 0.325% of the administered dose of radioactivity remaining after treatment with 50 or 400 mg/kg, respectively (Son et al., 1980). Small amounts of radioactivity were also found in kidneys, lungs, spleen, colon and bladder. Ring hydroxylation with subsequent conjugation appears to be the primary metabolic pathway for 2-methylaniline in the rat (Cheever et al., 1980), although oxidation of the methyl or amino group also occurs to a limited extent (Son et al., 1980). Approximately 85, 92 and 95% of the administered radioactivity was present in the urine of rats within 12, 24 and 72 hours, respectively, of a 50 mg/kg gavage dose of 2-methylaniline•HCl in distilled water (Cheever et al., 1980). Rats treated subcutaneously with ^{14}C-2-methylaniline excreted 79, 3.3 and 1.4% of the dose in the urine, feces and expired air within 48 hours (Son et al., 1980).

5. EFFECTS

5.1. CARCINOGENICITY

The carcinogenicity of 2-methylaniline•HCl was demonstrated in two chronic feeding studies using rats and mice (NCI, 1979; Weisburger et al., 1978) and in one chronic feeding study using rats (Hecht et al., 1982). Equivocal evidence of bladder cancer in 2-methylaniline-exposed workers has also been reported (IARC, 1982a).

In a study conducted by NCI (1979), groups of 50 male and 50 female F344 rats were fed diets containing 3000 or 6000 ppm 2-methylaniline•HCl (≥99% purity) for 104 or 101 weeks, respectively. Matched controls consisted of 20 male and 20 female rats maintained on basal diets for 104 weeks. Gross and comprehensive histological examinations were performed on all rats that died, that were killed when found moribund or that were killed at the end of the study, unless precluded by autolysis or cannibalism. There was a statistically significant dose-related increased mortality in both sexes. All high-dose males were dead at 101 weeks. The number of rats in the other groups surviving until 104 weeks was not reported.

As seen from Table 5-1, statistically significant, dose-related increased incidences (Cochran-Armitage test) of fibromas in subcutaneous tissue and sarcomas, fibrosarcomas, angirosarcomas and osteosarcomas in multiple organs occurred in male rats. The incidences of these tumors were significantly (Fisher Exact test) greater than control for both dose groups. The incidence of mesotheliomas in multiple organs were also significantly greater than control in low- and high-dose males, but the increase was not dose-related. Significantly dose-related increased incidences of fibroadenomas of the mammary gland, carcinomas and carcinoma or papilloma of the urinary bladder, sarcomas, fibrosarcomas, angiosarcomas or osteosarcomas of

TABLE 5-1

Summary of the Carcinogenicity of Dietary 2-Methylaniline·HCl (>99% purity)[a]

Species/ Strain	Sex	Dose (ppm)	Number of Animals	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence[b] (p value)[c,d]
Rat/F344	M	0	20	104	104	subcutaneous tissue	fibroma	0/20 (p=0.001)
						multiple organs	sarcoma, fibrosarcoma, angiosarcoma and osteosarcoma	0/20 (p<0.001)
						multiple organs or tunica vaginalis	mesothelioma	0/20 (NS)
Rat/F344	M	3000	50	104	104	subcutaneous tissue	fibroma	28/50 (p<0.001)
						multiple organs	sarcomas, fibrosarcomas, angiosarcomas and osteosarcoma	15/50 (p=0.003)
						multiple organs or tunica vaginalis	mesothelioma	17/50 (p=0.001)
Rat/F344	M	6000	50	101	101	subcutaneous tissue	fibroma	27/49 (p<0.001)
						multiple organs	sarcomas, fibrosarcomas, angiosarcomas and osteosarcoma	37/49 (p<0.001)
						multiple organs or tunica vaginalis	mesothelioma	9/49 (p=0.036)
Rat/F344	F	0	20	104	104	mammary gland	fibroadenomas	6/20 (p<0.001)
						urinary bladder	carcinoma	0/20 (p<0.001)
						urinary bladder	carcinoma or papilloma	0/20 (p<0.001)
						spleen	sarcomas, angiosarcomas, and osteosarcomas	0/20 (p=0.018)
						multiple organs	sarcomas, fibrosarcomas, angiosarcomas and osteosarcomas	0/20 (p<0.001)

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TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose (ppm)	Number of Animals	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence[b] (p value)[c,d]
Rat/F344	F	3000	50	104	104	mammary gland	fibroadenomas	20/50 (NS)
						urinary bladder	carcinoma	9/45 (p=0.028)
						urinary bladder	carcinoma or papilloma	10/45 (p=0.018)
						spleen	sarcomas, angiosarcomas, and osteosarcomas	9/49 (p=0.036)
						multiple organs	sarcomas, fibrosarcomas, angiosarcomas and osteosarcomas	3/50 (NS)
Rat/F344	F	6000	50	104	104	mammary gland	fibroadenomas	35/49 (p=0.002)
						urinary bladder	carcinoma	22/47 (p<0.001)
						urinary bladder	carcinoma or papilloma	22/47 (p<0.001)
						spleen	sarcomas, angiosarcomas, and osteosarcomas	12/49 (p=0.010)
						multiple organs	sarcomas, fibrosarcomas, angiosarcomas and osteosarcomas	21/49 (p<0.001)
Mouse/ B6C3F1	M	0	20	103	103	all sites	hemangiosarcomas hemangiosarcoma or hemangioma	1/19 (p=0.004) 1/19 (p=0.002)
	M	1000	50	103	103	all sites	hemangiosarcomas hemangiosarcoma or hemangioma	1/50 (NS) 2/50 (NS)
	M	3000	50	102	102	all sites	hemangiosarcomas hemangiosarcoma or hemangioma	10/50 (NS) 12/50 (NS)
Mouse/ B6C3F1	F	0	20	103	103	liver	hepatocellular carcinomas or adenomas hepatocellular carcinoma	0/20 (p=0.001) 0/20 (p=0.015)

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TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose (ppm)	Number of Animals	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence[b] (p value)[c,d]
Mouse/ B6C3F1	F	1000	50	103	103	liver	hepatocellular carcinomas or adenomas	4/49 (NS)
							hepatocellular carcinoma	2/49 (NS)
	F	3000	50	103	103	liver	hepatocellular carcinomas or adenomas	13/50 (p<0.007)
							hepatocellular carcinoma	7/50 (NS)

QUALITY OF EVIDENCE

Strengths of Study: Appropriate route of administration, adequate length of treatment and observation, two dose levels tested, two species tested, both males and females evaluated

Weakness of Study: High mortality in the high-dose male rats led to termination at 101 weeks

Overall Adequacy: Adequate

[a]Source: NCI, 1979

[b]Number of animals with tumors/number of animals examined at that site

[c]Cochran Armitage test results appear next to the incidence of tumors in control groups

[d]Fisher Exact test appear next to the incidence of tumors in treated groups

the spleen and of multiple organs occurred in female rats. The incidences of all of these tumors were significantly greater in the high-dose females than in controls, but only the incidences of urinary bladder and spleen tumors were also significantly higher in low-dose females than in controls. NCI (1979) concluded that 2-methylaniline•HCl was carcinogenic in both male and female rats.

The carcinogenic effect of 2-methylaniline•HCl (>99% of purity), administered in the diet for 102-103 weeks at 1000 or 3000 ppm, was also tested in groups of 50 male and 50 female B6C3F1 mice (NCI, 1979). Controls consisted of 20 male and 20 females. No increase in the mortality rate of the treated mice was observed and survival until the end of the study was 68-95% in all groups. As seen from Table 5-1, there was a statistically significant dose-related trend for increased incidence of hemangiosarcoma and for hemangioma or hemangiomasarcoma in male mice, but the increases were not significantly increased above controls for either group. Similarly, female mice had a statistically significant dose-related trend for increased incidences of liver tumors, but the incidences in the low- or high-dose group were not significantly greater than control. Nevertheless, NCI (1979) concluded that 2-methylaniline was carcinogenic in male and female mice.

In a recent re-analysis of the data generated by the NCI (1979) bioassay, Goodman et al. (1984) reported that 2-methylaniline•HCl, along with five other aromatic amines or their derivatives, was associated with the induction of splenic and peritoneal sarcoma. The authors postulated that exposure of rats to 2-methylaniline•HCl resulted in methemoglobinemia followed by splenic hemosiderosis, which induced splenic fibrosis, a preconditioning factor in the development of splenic sarcoma (fibrosarcoma,

osteosarcoma and hemangiosarcoma). Finally, according to the hypothesis suggested by Goodman et al. (1984), the splenic sarcoma developed into metastatic foci of neoplasia within the body cavities.

Weisburger et al. (1978) treated groups of 25 male Charles River CD (Sprague-Dawley derived) rats with 2-methylaniline•HCl in the diet at the MTD and at 1/2 the MTD. 2-Methylaniline•HCl was administered in the diet at 16,000 ppm for 3 months and 8000 ppm for the subsequent 15 months (TWA=9333 ppm) to the high-dose group or at 8000 ppm for 3 months and 4000 ppm for the subsequent 15 months (TWA=4667 ppm) to the low-dose group. Following the 18-month treatment period, rats were maintained for an additional 6 months on the control diet. There were 25 male matched control rats and 125 pooled control male rats. A complete gross necropsy was done on all rats that died after 6 months on test or were killed at the end of the study (24 months), with major organs, tumors and abnormal tissues being analyzed histologically. Statistical analysis was by the Fisher Exact test (the Cochran-Armitage test was not used). As summarized in Table 5-2, the incidence of subcutaneous fibromas and fibrosarcomas was significantly increased in both dose groups when compared with matched and pooled controls. The incidence of multiple tumors (simultaneous occurrence of fibromas or fibrosarcomas, pituitary adenomas, adrenal adenoma or transitional cell carcinoma of the bladder) was significantly higher in high-dose rats when compared with pooled controls. The incidence of transitional-cell carcinoma of the bladder increased in a dose-related manner, but the incidences in treated groups were not significantly different from matched or pooled controls.

TABLE 5-2

Summary of Carcinogenic Effects of Dietary Exposure to 2-Methylaniline·HCl (97-99% purity)[a]

Species/ Strain	Sex	Dose	Number of Rats	Duration of Treatment (months)	Duration of Study (months)	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
Rat/Charles River	M	0 (matched controls)	25	18	24	subcutaneous tissue	fibromas/ fibrosarcomas	0/16
						bladder	transitional cell carcinoma	0/16
						other	tumors (NOS)	3/16
	M	0 (pooled controls)	125	18	24	subcutaneous tissue	fibromas/ fibrosarcomas	18/111
						bladder	transitional cell carcinoma	5/111
						other	tumors (NOS)	14/111
	M	4667 ppm (TWA)	25	18	24	subcutaneous tissue	fibromas/ fibrosarcomas	18/23 (p<0.025)[c]
						bladder	transitional cell carcinoma	3/23
						other	tumors (NOS)	6/23
	M	9333 ppm (TWA)	25	18	24	subcutaneous tissue	fibromas/ fibrosarcomas	21/24 (p<0.025)[c]
						bladder	transitional cell carcinoma	4/24
						other	tumors (NOS)	8/24 (p<0.025)[d]
Mouse/CD-1 Albino	M	0 (matched controls)	25	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	0/14
	M	0 (pooled controls)	125	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	5/99

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TABLE 5-2 (cont.)

Species/ Strain	Sex	Dose	Number of Rats	Duration of Treatment (months)	Duration of Study (months)	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
Mouse/CD-1 Albino	M	3999 ppm (TWA)	25	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	5/14 (p<0.025)[c]
	M	18,667 ppm (TWA)	25	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	9/11 (p<0.025)[c]
	F	0 (matched controls)	25	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	0/15
	M	0 (pooled controls)	125	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	9/102
	M	9333 ppm (TWA)	25	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	5/18 (p<0.025)[c,d,e]
	M	18,667 ppm (TWA)	25	18	24	abdominal viscera	hemangioma/ hemangiosarcoma	9/21 (p<0.025)[c]

QUALITY OF EVIDENCE

Strengths of Study: Appropriate route of administration, adequate length of treatment and observation, two species tested, both male and female mice evaluated

Weakness of Study: Only male rats were evaluated; animals that died during the first 6 months were not necropsied.

Overall Adequacy: Adequate

[a]Source: Weisburger et al., 1978

[b]Fisher Exact test

[c]Compared with both matched and pooled controls

[d]Compared with pooled controls only

[e]Compared with matched controls only

NOS = Not otherwise specified

In addition, Weisburger et al. (1978) treated groups of 25 male and 25 female albino CD-1 (HaM/ICR derived) mice with 2-methylaniline•HCl at 32,000 ppm for 3 months and then a 16,000 ppm for an additional 15 months (TWA=18,667 ppm) or 16,000 ppm for 3 months and then 8000 ppm for 15 additional months (TWA=9333 ppm). Both groups were maintained for 3 months on control diets after the 18-month treatment period. Controls consisted of 25 male and 25 female matched controls and 125 male and 125 female pooled controls. Gross necropsy and histology of major organs, tumors and abnormal tissues were performed on all mice that died after 6 months on test or were killed at the end of the 21-month study period. In both male and female mice, significant incidences of hemangiosarcomas and hemangiomas occurred in viscera of the abdomen (see Table 5-2).

Hecht et al. (1982) demonstrated the carcinogenicity of 2-methylaniline•HCl by dietary administration to F344 rats in a study designed to compare the carcinogenicity of 2-methylaniline•HCl and one of its metabolites, o-nitrosotoluene. One group of 30 male rats ingested dietary 2-methylaniline•HCl at a dose of 62 mg/rat/day (0.43 mmol/rat/day) for 72 weeks. The average weight of these rats was ~0.454 kg; therefore, the dosage was ~136.6 mg/kg/day. Another group of 30 male rats served as controls, while a third group of 30 male rats was treated with dietary o-nitrosotoluene at 51 mg/rat/day (0.42 mmol/rat/day). The average weight of these rats was ~0.34 kg; therefore, the dose was ~150 mg/kg/day. After an observation period of an additional 20 weeks, all surviving rats were killed. On histopathological examination, a number of tumors were observed in treated rats (Table 5-3). Incidences of skin fibroma, spleen fibroma, mammary fibroadenoma and peritoneum sarcoma were significantly increased in treated rats compared with controls. Other tumor incidences evaluated were

TABLE 5-3

Incidence of Tumors in Male F344 Rats Treated with 2-Methylaniline•HCl (purity NR) in the Diet for 73 Weeks and Observed for an Additional 93 Weeks[a]

Dose (mg/kg/day)	No. of Rats	Target Organ	Tumor Type	Tumor Incidence (p value)[b]
0	30	skin	fibroma	1/27[c]
		spleen	fibroma	0/27
		mammary gland	fibroadenoma	0/27
		peritoneum	sarcoma	0/27
136.6	30	skin	fibroma	25/30 (p<0.001)
		spleen	fibroma	10/30 (p<0.001)
		mammary gland	fibroadenoma	11/30 (p<0.001)
		peritoneum	sarcoma	9/30 (p=0.0016)

QUALITY OF EVIDENCE

Strengths of Study: Appropriate route of administration, adequate length of treatment and observation

Weakness of Study: Only one dose tested, only males evaluated

Overall Adequacy: Limited

[a]Source: Hecht et al., 1982

[b]The Chi square test was used to evaluate the difference in carcinogenic effects caused by 2-methylaniline and o-nitrostoluene, but no p-value were reported by Hecht et al. (1982) in comparisons between treated and control groups. The p values listed are from the Fisher Exact Test performed at SRC.

[c]Only 27/30 control rats were necropsied. No reason was given.

liver hepatomas and adenomas, bladder papillomas and carcinomas and Leydig testicular tumors, but these latter tumors were not induced by 2-methylaniline. o-Nitrosotoluidine also induced skin and spleen fibromas, but unlike 2-methylaniline, appeared to increase the incidences of liver hepatomas and bladder papillomas (data not shown).

Morigami and Nisimura (1940) subcutaneously injected 15 rabbits with 1 mL/rabbit/application and 10 guinea pigs with 0.5 mL/guinea pig/application of a 2% solution of 2-methylaniline in olive oil, 6 times/week. The animals were sacrificed at various intervals and histological examinations revealed a progression of bladder lesions. After 100 days, papillomas in the bladder epithelium were observed in rabbits. The guinea pigs also had bladder lesions, but they died before papillomas developed. Other pertinent details were not provided. Morigami and Nisimura (1940) also applied an unspecified quantity of a 0.5% solution of 2-methylaniline to the skin of an unspecified number of rats, every other day. The duration was not reported. Histological examination revealed hemorrhage, atrophy and papillomas in the bladder epithelium. Additional details were not provided.

IARC (1982a) reviewed a study by Satani et al. (1941), in which bladder papillomas developed in 1/2 rats and 4/5 rabbits treated with 2-methylaniline in olive oil or alcohol subcutaneously. Additional details were not provided.

In a study summarized by Du Pont de Nemours and Co. (1983), a dose of 100 mg/day of 2-methylaniline was administered to five female dogs in their diet, 5 days/week for 5 or 6 years (Deichman, 1967). Two dogs died after 1-2 years, but the ages of the dogs at the start of treatment were not reported. No effects on the urinary bladders of the remaining three dogs were observed after 5-6 years of treatment. These dogs received a total dose of 126 or 153 g. No other parameters of toxicity were reported.

A number of human case reports and epidemiological studies have reported bladder cancer in workers in the dyestuff industry (Case and Pearson, 1954; Case et al., 1954; Oettel, 1959, 1967; Oettel et al., 1968; Uebelin and Pletscher, 1954; Gropp, 1958; Vigliani and Barsotti, 1961; Zavon et al., 1973; Khlebnikova et al., 1970; Lipkin, 1972; Genin et al., 1978; Rubino et al., 1982). In these studies, workers were exposed to a variety of other potential bladder and other carcinogens [e.g., benzidine, 4,4'-methylene-bis(2-methylaniline), 2-naphthylamine, aniline]; insufficient details were provided regarding person-years at risk and follow-up to evaluate the significance. IARC (1982a) concluded that in these studies, 2-methylaniline "cannot be identified specifically as the responsible agent" for the increased incidence of bladder tumors.

5.2. MUTAGENICITY

There have been a number of studies investigating the genotoxicity of 2-methylaniline (Table 5-4). 2-Methylaniline has been tested and shown not to be mutagenic in the reverse mutation assay using histidine-dependent strains of Salmonella typhimurium. These negative results were obtained both with and without the addition of a mammalian metabolic activation system. The only positive mutagenic response obtained with S. typhimurium was in the assay performed by Nagao et al. (1978) in which norharman (9H-pyridol[3,4-b]indole) was added to the assay system. (The mechanism by which norharman facilitates the mutagenicity of other compounds is not known.) In addition, Tanaka et al. (1980) reported that ether extracts of urine from rats given an oral dose of 2-methylaniline were mutagenic in S. typhimurium only in the presence of mammalian metabolic activation.

TABLE 5-4

Mutagenicity of 2-Methylaniline

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	S. typhimurium TA1538	plate incorporation	50, 100 µg/plate	+/-	-/-	Garner and Nutman, 1977
Reverse mutation	S. typhimurium TA1538, TA1537 TA1538, TA98, TA100	plate incorporation	1000 µg/plate	+/-	-/-	Simmon, 1979a
Reverse mutation	S. typhimurium TA100, TA98, TA1537	plate incorporation	NR	+/-	-/-	Zimmer et al., 1980
Reverse mutation	S. typhimurium TA100, TA98, TA1537, TA1535	plate incorporation	10 mg/plate	+/-	-/-	McCann et al., 1975
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	0.03-30 µmol/plate	+/-	-/-	Florin et al., 1980
Reverse mutation	S. typhimurium TA1535, TA1538	plate incorporation	250 µg/plate	+/-	-/-	Rosenkranz and Poirier, 1979
Reverse mutation	S. typhimurium TA1538	plate incorporation	100 µg/plate	+/-	-/-	Ferretti et al., 1977
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	50-1000 µg/plate	+/-	-/-	Tanaka et al., 1980
Reverse mutation	S. typhimurium TA98	plate incorporation	50 µg/plate	+/-	-/-	Nagao et al., 1978
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	NR	+/-	-/-	Nohmi et al., 1984
Reverse mutation	S. typhimurium G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, TA98	plate incorporation	up to 1000 µg/mL	+/-	-/-	Thompson et al., 1983
Reverse mutation	S. typhimurium TA98	plate incorporation	50 µg/plate	+/-	-/-[a]	Nagao et al., 1978

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TABLE 5-4 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	spot test	3 µmol/plate	±	-	Florin et al., 1980
Reverse mutation	E. coli WP2uvrA⁻	plate incorporation	up to 1000 µg/mL	+/-	-/-	Thompson et al., 1983
Rec assay	E. coli pol A⁻, pol A⁺	liquid suspension	0.5 µg/mL	-	+	Rosenkranz and Poirer, 1979
Rec assay	E. coli pol A⁻, pol A⁺	disc	20 µL/plate	-	-	Rosenkranz and Poirer, 1979; Rosenkranz and Liefer, 1980
Prophage induction	E. coli K 12	NR	NR	-	+	Galkiewicz et al., 1979
Mitotic recombination	S. cerevisiae D3	liquid suspension	0.8%	+/-	-	Simmon, 1979b
DNA damage	Chinese Hamster lung fibroblasts	liquid holding	0.3-10 mM for 2 hours	+	-	Zimmer et al., 1980
Unscheduled DNA synthesis	hamster and rat hepatocytes	primary cell culture	NR	NR	NA	Kornbrust and Barfknecht, 1984
Unscheduled DNA synthesis	rat hepatocytes	primary cell culture	up to 500 µmol/mL	NA	-	Thompson et al., 1983
Cell transformation	leukemia virus infected AKR NIH Swiss mouse embryo cells	plate incorporation	1, 10 µg/mL	-	+	Rhim et al., 1974
SCE	Chinese Hamster bone marrow	gavage, intraperitoneal injection	200, 300 mg/kg	NA	+	Neal and Probst, 1983
SCE	Chinese Hamster[b] ovary cells (in vitro)	plasma from treated rats	400 mg/kg to rat i.p.	45 minutes in rat[b]	+	Darroudi and Natarajan, 1985

TABLE 5-4 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Forward mutation	L5178Y TK+/- mouse lymphoma cells	cell culture medium	125-650 µg/ml +S9 600-1300 µg/ml -S9	+/-	-/-	Oberly et al., 1984
Sperm head abnormalities	CBA/BALB/C mice	intraperitoneal injection 5 injections/day	0.05-0.5 mg/kg/day	NA	-	Topham, 1980
Testicular DNA synthesis	mice	gavage	200 mg/kg	NA	+	Seller, 1977

[a]When norharman and S-9 are added with 2-methylaniline, an increased frequency of mutations was observed.

[b]This assay was performed in two steps. First, rats were injected intraperitoneally with 2-methylaniline. Within 45 minutes plasma was obtained from the 2-methylaniline treated rats incubated with Chinese hamster ovary cells in vitro for 16 hours. The frequency of SCE was determined in the Chinese hamster ovary cells.

NA = Not applicable; NR = not reported

In other assay systems 2-methylaniline has produced mixed results. In the absence of an activation system, 2-methylaniline has produced positive results in the selective inhibition of growth in DNA repair-deficient strains of Escherichia coli when assayed in liquid media (Rosenkranz and Poirier, 1979), but not when the compound was allowed to diffuse into the media from filter discs (Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980). In another assay using E. coli K12, 2-methylaniline stimulated the induction of prophage (Galkiewicz et al., 1979). In eukaryotic systems 2-methylaniline has caused cell transformations in virus-infected mouse cells in culture (Rhim et al., 1974). The frequency of SCE was increased in Chinese hamster ovary cells cultivated for 16 hours in medium containing plasma obtained from rats 45 minutes after they had received an intraperitoneal injection of 400 mg/kg of 2-methylaniline (Darroudi and Natarajan, 1985). Other assays in eukaryotic systems have failed to demonstrate that 2-methylaniline produces mitotic recombination in yeast (Simmon, 1979b) or DNA breaks in cultured mammalian cells (Zimmer et al., 1980).

Following in vivo exposure of mice to 2-methylaniline, thymidine incorporation into testicular DNA was inhibited (Seiler, 1977). The frequency of SCE increased in hamster bone marrow cells after in vivo exposure (Neal and Probst, 1983). No increase in abnormal sperm heads, however, was observed after the intraperitoneal injection of mice with 2-methylaniline (Topham, 1980).

In addition to the studies cited above, two international collaborative studies employing large numbers of short-term mutagenicity tests evaluated 2-methylaniline. In the first (Ashby, 1981), 42 separate tests were performed with generally negative results observed in bacterial mutation

assays (12 of 19 tests). In eukaryotic systems positive results were seen for unscheduled DNA synthesis, sister-chromatid exchange and *in vitro* morphological transformation tests.

The second collaborative study selected chemicals that were classified as carcinogens but were generally negative in the standard *Salmonella* assay (Ashby et al., 1985). The aim was to determine whether: 1) there were technical inadequacies of the *Salmonella* assay, 2) the carcinogen had a specificity of genetic activity, or 3) there was an absence of genetic activity implying a nongenotoxic mechanism of carcinogenesis. All tests used were *in vitro* tests and the majority (53/84) were tests measuring a variety of endpoints in higher eukaryotes. Consistent with all earlier work, 2-methylaniline was negative in *Salmonella* but generally positive in higher organisms (30 of the 53 tests were positive). Since positive effects were observed for essentially all types of genetic lesions (gene mutations, chromosome aberrations, unscheduled DNA synthesis, sister-chromatid exchange, DNA strand breaks, etc.) the authors concluded that 2-methylaniline is a general or classical genotoxin that requires specific metabolic activation. In this regard, it is noteworthy that the single positive result observed in *Salmonella* was that in which hamster liver was the source of the S-9 activating system.

5.3. TERATOGENICITY

Although pertinent experimental data specifically regarding the teratogenicity of 2-methylaniline or 2-methylaniline•HCl could not be located in the available literature, two reports (Meyers, 1983; Golub et al., 1974) are of interest. Meyers (1983) suggested that 2-methylaniline may be a teratogen based on the similarity between the chemical structure and biological

activity of 2-methylaniline and other known teratogens. Although 2-methylaniline is a suspected teratogen according to these criteria, classification of teratogens by biological activity and chemical structures is likely to produce many false positives.

The abstract of a Russian study (Golub et al., 1974) reported an increased frequency of tumor development in the offspring of BALB/c mice treated with four or five subcutaneous injections (total of 2 mg/mouse) of 2-methylaniline during the last week of gestation. The age of the offspring at the termination of the experiment was not reported, and no further details were given.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent oral or inhalation data regarding other reproductive effects of 2-methylaniline or 2-methylaniline·HCl could not be located in the available literature as cited in the Appendix. The absence of sperm head abnormalities, however, was reported in CBA/BALB/c mice after treatment with five intraperitoneal injections of 2-methylaniline totaling 0.05-0.5 mg/kg (Topham, 1980).

Two abstracts of Russian studies (Malysheva and Zaitseva, 1982; Malysheva et al., 1983) reported that 8 mg/kg of 2-methylaniline applied 4 hours/day to the tails of white rats for 4 months increased corpora lutea and atresia, increased the duration of estrus, stimulated spermatogenesis, and adversely affected the offspring of treated males or treated females.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In a series of experiments, Strombeck (1946) and Ekman and Strombeck (1947, 1949) studied the effect of dietary 2-methylaniline on the urinary bladder of rats.

All 10 rats that received a rice flour and carrot diet supplying 15-24 mg of 2-methylaniline/day for 64 days followed by a similar diet supplying 7.5-12 mg of 2-methylaniline/day were dead 91 days after the start of treatment (Strombeck, 1946; Ekman and Strombeck, 1947). The sex and the age of the rats at the start of the experiment were not reported. No controls were reported. Mucous membrane metaplasia and epithelial proliferation were observed in 3/10 rats in the experiment. In a second experiment, Ekman and Strombeck (1949) gave groups of six male and six female rats diets containing various amounts of riboflavin, ascorbic acid and 0 or 0.1% 2-methylaniline for 135-341 days. Examination of the urinary bladders of these rats showed effects ranging from epithelial metaplasia with cornification and proliferation, "a tendency to form papillomas," to atypical epithelium. These bladder lesions were observed in 10/26 rats given 2-methylaniline. Thickening of the bladder mucosal epithelium without proliferation was observed in the bladders of 2/7 control rats.

Primarily neoplastic effects were observed in a 104-week chronic feeding study performed to assess the carcinogenicity of 2-methylaniline•HCl in rats and mice (NCI, 1979) (see Section 5.1.); however, the frequency of several nonneoplastic lesions was significantly increased in the rats ingesting 2-methylaniline•HCl. Both male and female rats had a dose-related increased mortality rate and a decreased body weight gain. In addition, there were increased incidences of splenic fibrosis, myocardial fibrosis, liver necrosis and urinary bladder epithelial hyperplasia in male rats and liver necrosis and urinary bladder epithelial hyperplasia in female rats. The incidences and statistical significance of these lesions are summarized in Table 5-5. The biological significance of the hyperplastic changes in the spleen may be closely related to the increased incidence of splenic tumors in both male and female rats and may represent preneoplastic lesions.

TABLE 5-5

Incidence of Nonneoplastic Lesions in F344 Rats
Ingesting 2-Methylaniline·HCl[a]

Lesion	Incidence (p value)[b]		
	Control	Low Dose	High Dose
Male Rats			
Splenic fibrosis	0/20 (NS)	13/49 (0.007)	5/42 (NS)
Myocardial fibrosis	0/20 (NS)	17/50 (0.001)	8/48 (0.051)
Liver necrosis	2/20 (0.031)	12/50 (NS)	17/49 (0.032)
Urinary bladder hyperplasia	0/20 (NS)	9/50 (0.039)	7/44 (NS)
Female Rats			
Mesothelial hyperplasia of splenic capsule	0/20 (NS)	32/49 (<0.001)	12/49 (0.010)
Liver necrosis	0/20 (<0.001)	1/49 (NS)	15/49 (0.003)
Urinary bladder hyperplasia	0/20 (NS)	21/45 (<0.001)	13/47 (0.006)

[a]Source: NCI, 1979

[b]The values listed beside the incidences in the treated group are the p values from a Fisher Exact test, while the values listed beside the control incidence are the p values for the Cochran-Armitage test for linear trend. The statistical tests were performed at SRC.

NS = Not significant

The incidence of myocardial fibrosis was significantly increased in the low-dose male rats, and marginally increased in the high-dose male rats. The biological significance of myocardial fibrosis that is due to 2-methylaniline ingestion, however, may be compounded by the methemoglobinemic effects (see Section 5.6.) of 2-methylaniline. The myocardial effect of 2-methylaniline was not observed in female rats. On the other hand, the increased incidence of urinary bladder epithelial hyperplasia and urinary bladder tumors was much more pronounced in female rats (see Section 5.1.). A progression from transitional cell epithelial hyperplasia to transitional cell carcinoma of the urinary bladder appeared to be dose-related in the females. A significant increase in the incidence of liver necrosis was observed at the high-, but not the low-dose group in both male and female rats.

No significant increase in the incidence of nonneoplastic lesions was observed in the mice ingesting 2-methylaniline•HCl; however, the body weight gains of both male and female mice were significantly decreased in both dose groups and the decrease was dose-related (NCI, 1979).

No compound-related, nonneoplastic effects were reported to result from the chronic feeding of 2-methylaniline•HCl to rats and mice in the carcinogenicity study by Weisburger et al. (1978) (see Section 5.1.).

5.6. OTHER RELEVANT INFORMATION

The LD_{50} values for 2-methylaniline and 2-methylaniline•HCl are listed in Tables 5-6 and 5-7, respectively.

Groups of 20 and 30 male F344 rats were treated by gavage (no vehicle) with 0 or 225 mg/kg/day of 2-methylaniline, respectively (Short et al., 1983). Groups of 10 control and 6 or 8 2-methylaniline-exposed rats were killed 5, 10 and 20 days after the start of treatment. The body weights of

TABLE 5-6

LD_{50} Values for 2-Methylaniline

Species	Route	LD_{50} Value (mg/kg)	Reference
Rat	oral (gavage, no vehicle)	900	Short et al., 1983
Rat	oral	900	Jacobson, 1972
Rat	oral	670	Lunkin, 1967
Rat	oral	940	Smyth et al., 1962
Mouse	oral	515	Lunkin, 1967
Cat	oral	300	NIOSH, 1986
Rabbit	oral	844	Lunkin, 1967
Rabbit	dermal	3250	Smyth et al., 1962
Mouse	intraperitoneal	150	NIOSH, 1986

TABLE 5-7

LD_{50} Values for 2-Methylaniline•HCl

Species	Route	LD_{50} Value (mg/kg)	Reference
Rat	oral	2951	NIOSH, 1986
Mouse	oral	1100	NIOSH, 1986
Rat (male)	intraperitoneal	164	Weisburger et al., 1978
Rat (female)	intraperitoneal	246	Weisburger et al., 1978
Mouse (male)	intraperitoneal	179	Weisburger et al., 1978
Mouse (female)	intraperitoneal	113	Weisburger et al., 1978
Rat	intraperitoneal	150	NIOSH, 1986
Mouse	intraperitoneal	113	NIOSH, 1986

the treated rats were significantly lower than that of the control rats 5 and 10 days, but not 20 days after the start of treatment. The splenic weight in the 2-methylaniline-treated rats was significantly higher at 5, 10 and 20 days after treatment than the splenic weight in age-matched control rats. Both hemosiderosis and hematopoiesis were increased in the spleens of rats treated with 225 mg/kg/day of 2-methylaniline. In addition, mild renal hemosiderosis and increased density of bone marrow cells were observed in the rats treated with 2-methylaniline. No adverse histological effects were observed in the liver, esophagus, trachea, thyroid, parathyroid or urinary bladder of rats treated with 2-methylaniline for up to 20 days.

Methemoglobinemia has been reported in cats after intravenous administration of 0.25 mmol/kg (27 mg/kg) 2-methylaniline (McLean et al., 1969), in rats after intragastric administration of an unspecified dose of 2-methylaniline (Senczuk and Rucinska, 1984c) and in mice after intraperitoneal injection of 2-methylaniline (Smith et al., 1967). Goldstein et al. (1963) suggested that, based on experimental data from rats, rabbits and dogs, the measurement of sulfhemoglobin levels, rather than methemoglobin levels, may be a better indicator of 2-methylaniline exposure. In addition, they reported that catalase and succinic dehydrogenase activity decreased, while cytochrome oxidase activity increased, in rats, rabbits and dogs exposed to 2-methylaniline.

Repeated administration of 2-methylaniline can cause methemoglobinemia, appetite loss and fatigue (ACGIH, 1986), as well as increased aryl hydrocarbon hydroxylase activity levels in the liver, lung and particularly in the kidney (Gnojkowski et al., 1984).

5.7. SUMMARY

2-Methylaniline•HCl was carcinogenic in both rats and mice (NCI, 1979; Weisburger et al., 1978; Hecht et al., 1982). The NCI (1979) reported increased incidences of multiple site sarcomas, subcutaneous fibromas and multiple site mesotheliomas in male rats; multiple site sarcomas, mammary fibroadenomas, splenic sarcomas and urinary bladder carcinomas or papillomas in female rats; multiple site hemangiosarcomas in male mice; and hepatocellular carcinomas or adenomas in female mice ingesting dietary 2-methylaniline•HCl. Weisburger et al. (1978) reported an increased incidence of tumors, subcutaneous fibromas/fibrosarcomas and urinary bladder transitional cell carcinomas in male rats and abdominal visceral hemangiomas/hemangiosarcomas in both male and female mice ingesting dietary 2-methylaniline•HCl. Hecht et al. (1982) reported an increased incidence of subcutaneous and splenic fibromas, peritoneal sarcomas and mammary gland fibroadenomas in male rats ingesting dietary 2-methylaniline•HCl. 2-Methylaniline has been the subject of an extensive number of mutagenicity tests including two international collaborative studies (Ashby, 1981; Ashby et al., 1985). Almost universally, negative results have been observed in Salmonella with the notable exception in the case when hamster liver (rather than rat liver) was the source of exogenous metabolic activation. Positive results have been observed in a variety of mammalian in vitro systems capable of detecting gene mutations, single-strand DNA breaks, unscheduled DNA synthesis, sister-chromatid exchange, chromosome aberrations and morphological transformation. Based upon these findings, Ashby et al. (1985) concluded that 2-methylaniline is a general genotoxin that requires specific metabolic activation. No information on the developmental or reproductive

effects of ingested or inhaled 2-methylaniline and 2-methylaniline·HCl were available. Meyers (1983) suggested, however, that 2-methylaniline may be teratogenic based on the similarity between the chemical structure and biological activity of 2-methylaniline and other known teratogens. Increased incidences of offspring of mice injected subcutaneously during gestation with 2-methylaniline have been reported in a Russian study (Golub et al., 1974). The noncarcinogenic effects of chronic ingestion of 2-methylaniline·HCl by rats included decreased lifespan at 3000 and 6000 ppm, decreased body weight gain at both doses and liver necrosis at the high dose in both males and females, myocardial fibrosis in males and urinary bladder hyperplasia in females at both doses (NCI, 1979). Rats receiving diets supplying 2-methylaniline at dosages of 15-24 mg/rat/day for 64 days followed by 7.5-12 mg/rat/day died by day 91 and had mucous membrane metaplasia and epithelial hyperplasia in the urinary bladder (Strombeck, 1946; Ekman and Strombeck, 1947). Similar bladder lesions occurred in rats maintained on diets containing 0.1% (1000 ppm) 2-methylaniline for up to 341 days (Ekman and Strombeck, 1949). Although not evaluated in any of the chronic studies with 2-methylaniline·HCl, increased methemoglobin levels occurred in rats, cats, mice, rabbits and dogs after short-term (1 day to several weeks) exposure to 2-methylaniline (Short et al., 1983; McLean et al., 1969; Senczuk and Rucinska, 1984c; Smith et al., 1967; Goldstein et al., 1963).

6. AQUATIC TOXICITY

6.1. ACUTE

The available data concerning acute toxicity of 2-methylaniline to aquatic animals are presented in Table 6-1. The most sensitive species tested was Daphnia magna, with a 24-hour LC_{50} value of 26 mg/ℓ (Bringmann and Kuehn, 1977) and a "toxicity threshold" of 2 mg/ℓ (Smirnova et al., 1967). The ciliate protozoan, Uronema parduczi, was the next most sensitive species with a toxicity threshold of 21 mg/ℓ (Bringmann and Kuehn, 1981). Pertinent data regarding the acute toxicity of 2-methylaniline•HCl could not be located in the available literature as cited in the Appendix.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of 2-methylaniline and 2-methylaniline•HCl to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Bringmann and Kuehn (1978, 1980) reported toxicity thresholds for inhibition of cell multiplication in various algae and bacteria. These values were 6.3 mg/ℓ for the green alga, Scenedesmus quadricauda, 0.31 mg/ℓ for the blue-green alga, Microcystis aeruginosa, and 16 mg/ℓ for the bacterium, Pseudomonas putida. In a study using the algal lawn technique, growth of the blue-green alga, Agmenellum quadruplicatum, was unaffected by 0.1 and 1.0 µg/dish, partially inhibited by 10 µg/dish and completely inhibited by ≥100 µg/dish (Batterton et al., 1978). In similar algal lawn bioassays, growth of green alga Chlorella autotrophica was unaffected by 0.5 mg/dish, partially inhibited by 1 and 2 mg/dish, and completely inhibited by 10 mg/dish. Growth of Cylindrotheca sp. was partially inhibited by 0.5, 1 and 2 mg/dish and completely inhibited by 10 mg/dish (Winters et al., 1976).

TABLE 6-1

Acute Toxicity of 2-Methylaniline to Fish and Aquatic Invertebrates

Species	Concentration (mg/l)	Effect	Reference
FISH			
Golden orfe (*Leuciscus idus*)	30	48-hour LC_0	Juhnke and Luedemann, 1978
	117	48-hour LC_{50}	Juhnke and Luedemann, 1978
	178	48-hour LC_{100}	Juhnke and Luedemann, 1978
Guppy (*Poecilia reticulata*)	200	no mortality	Smirnova et al., 1967
	500	100% mortality in 2-4 minutes	Smirnova et al., 1967
Fathead minnow (*Pimephales promelas*)	60	NOAEL	Dow Chemical Co., 1983
CRUSTACEANS			
Waterflea (*Daphnia magna*)	2.5	24-hour LC_0	Bringmann and Kuehn, 1977
	26	24-hour LC_{50}	Bringmann and Kuehn, 1977
	60	24-hour LC_{100}	Bringmann and Kuehn, 1977
	20	100% mortality	Smirnova et al., 1967
	2	toxicity threshold	Smirnova et al., 1967
	1.6-5.0	24-hour EC_0, immobilization	Bringmann and Kuehn, 1982
	9-50	24-hour EC_{50}, immobilization	Bringmann and Kuehn, 1982
	100	24-hour EC_{100}, immobilization	Bringmann and Kuehn, 1982
Amphipod (*Elasmopus pectenicrus*)	>40	96-hour LC_{50}	Lee and Nicol, 1978
MOLLUSCS			
Mussel (*Mytilus edulis*)	500	100% mortality, 72 hours	Knezovich and Crosby, 1985
	250	67% mortality, 96 hours	Knezovich and Crosby, 1985
	100	no mortality, 96 hours	Knezovich and Crosby, 1985
Oyster (*Crassostrea gigas*)	500	100% mortality, 72 hours	Knezovich and Crosby, 1985
	250	67% mortality, 96 hours	Knezovich and Crosby, 1985
	100	no mortality, 96 hours	Knezovich and Crosby, 1985
PROTOZOA			
Flagellate (*Entosiphon sulcatum*)	76	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Flagellate (*Chilomonas paramecium*)	237	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Ciliate (*Uronema parduczi*)	21	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Ciliate (*Tetrahymena pyriformis*)	200	24-hour LC_{100}	Schultz et al., 1978

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6.4. RESIDUES

Knezovich and Crosby (1985) studied uptake and elimination of radiolabeled 2-methylaniline by mussels, Mytilus edulis, and oysters, Crassostrea gigas, exposed to 5 mg/ℓ. They found that uptake from water was rapid, with steady-state achieved in 4 hours. BCFs for 24-hour exposures were 4.6 for oysters and 4.2 for mussels. The primary site of accumulation in both species were the gills. Elimination was rapid with 85 and 92% of the body burden eliminated by oysters and mussels, respectively, in a 4-hour depuration period. N-Oxidized, N-methyl and N-formyl metabolites were formed by these molluscs, but most of the excreted radioactivity was in the form of the parent compound.

Knezovich and Crosby (1986) conducted a similar study with red abalone Haliotis rufescens, and starry flounder, Platichthys stellatus, exposed to 5 mg/ℓ for 4 hours. BCFs after 4 hours were 4.4 for the abalone and 2.6 for the flounder, corresponding to body burdens of 21.9 and 10.2 µg/g, respectively. After 4 hours in uncontaminated water, the abalone retained 13.2% of its body burden (2.9 µg/g), and the flounder retained 18.6% (1.9 µg/g); >99% of the eliminated radioactivity was still in the form of the parent compound.

6.5. SUMMARY

LC_{50} values of 117 and 26 mg/ℓ 2-methylaniline were reported for the golden orfe (Juhnke and Luedemann, 1978) and Daphnia magna. The blue-green alga, Microcystis aeruginosa, with a toxicity threshold of 0.31 mg/ℓ, was more sensitive than Scenedesmus quadricauda (6.3 mg/ℓ) or Pseudomonas putida (16 mg/ℓ) (Bringmann and Kuehn, 1978, 1980). Pharmacokinetics studies with three marine molluscs and one fish species indicated that uptake of 2-methylaniline was rapid and steady-state was achieved in 4

hours; however, since elimination was also rapid, BCFs were <5 for all four species. Almost all radioactivity excreted by these species was in the form of the parent compound, indicating that they do not metabolize 2-methylaniline to a great extent (Knezovich and Crosby, 1985, 1986).

Pertinent data regarding the aquatic toxicity of 2-methylaniline•HCl could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits for 2-methylaniline·HCl could not be located in the available literature as cited in the Appendix.

The OSHA (1985) standard for occupational exposure to 2-methylaniline requires that concentrations in air not exceed 5 ppm (22 mg/m³) (22 mg/m³) for an 8-hour TWA.

ACGIH (1986) recommends an 8-hour TLV for 2-methylaniline of 2 ppm (9 mg/m³) for an 8-hour TWA to protect workers from clinical signs of intoxication, including methemoglobinemia, cyanosis, hematuria, renal and bladder irritation and other unspecified physiological and psychological disturbances. ACGIH (1986) has given 2-methylaniline an A-2 classification, meaning that this compound is a suspect carcinogen for man. ACGIH (1986) has given 2-methylaniline a SKIN notation, which means that the substance can contribute to the overall exposure by the cutaneous route.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of 2-methylaniline and 2-methylaniline·HCl could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

2-Methylaniline•HCl was carcinogenic in both rats and mice (NCI, 1979; Weisburger et al., 1978; Hecht et al., 1982). The NCI (1979) reported increased incidences of multiple site sarcomas, subcutaneous fibromas and multiple site mesotheliomas in male rats; multiple site sarcomas, mammary fibroadenomas, splenic sarcomas and urinary bladder carcinomas or papillomas in female rats; multiple site hemangiosarcomas in male mice; and hepatocellular carcinomas or adenomas in female mice ingesting dietary 2-methylaniline•HCl. Weisburger et al. (1978) reported an increased incidence of tumors (NOS), subcutaneous fibromas/fibrosarcomas and urinary bladder transitional cell carcinomas in male rats and abdominal visceral hemangiomas/hemangiosarcomas in both male and female mice ingesting dietary 2-methylaniline•HCl. Hecht et al. (1982) reported an increased incidence of subcutaneous and splenic fibromas, peritoneal sarcomas and mammary gland fibroadenomas in male rats ingesting dietary 2-methylaniline•HCl. 2-Methylaniline has been the subject of an extensive number of mutagenicity tests including two international collaborative studies (Ashby, 1981; Ashby et al., 1985). Almost universally, negative results have been observed in Salmonella with the notable exception in the case when hamster liver (rather than rat liver) was the source of exogenous metabolic activation. Positive results have been observed in a variety of mammalian in vitro systems capable of detecting gene mutations, single-strand DNA breaks, unscheduled DNA synthesis, sister-chromatid exchange, chromosome aberrations and morphological transformation. Based upon these findings, Ashby et al. (1985) concluded that 2-methylaniline is a general genotoxin that requires specific metabolic activation. No information on the developmental and reproductive

effects of ingested or inhaled 2-methylaniline and 2-methylaniline•HCl were available. Meyers (1983) suggested, however, that 2-methylaniline may be teratogenic based on the similarity between the chemical structure and biological activity of 2-methylaniline and other known teratogens. Increased incidences of offspring of mice injected subcutaneously during gestation with 2-methylaniline have been reported in a Russian study (Golub et al., 1974). The noncarcinogenic effects of chronic ingestion of 2-methylaniline•HCl by rats included decreased lifespan at 3000 and 6000 ppm, decreased body weight gain at both doses and liver necrosis at the high dose in both males and females, myocardial fibrosis in males and urinary bladder hyperplasia in females at both doses (NCI, 1979). Rats receiving diets supplying 2-methylaniline at dosages of 15-24 mg/rat/day for 64 days followed by 7.5-12 mg/rat/day died by day 91 and had mucous membrane metaplasia and epithelial hyperplasia in the urinary bladder (Strombeck, 1946; Ekman and Strombeck, 1947). Similar bladder lesions occurred in rats maintained on diets containing 0.1% (1000 ppm) 2-methylaniline for up to 341 days (Ekman and Strombeck, 1949). Although not evaluated in any of the chronic studies with 2-methylaniline•HCl, increased methemoglobin levels occurred in rats, cats, mice, rabbits and dogs after short-term (1 day to several weeks) exposure to 2-methylaniline (Short et al., 1983; McLean et al., 1969; Senczuk and Rucinska, 1984c; Smith et al., 1967; Goldstein et al., 1963).

NCI (1979) provided probably the best evidence for 2-methylaniline•HCl carcinogenicity in rats. Groups of 50 male and 50 female F344 rats were fed diets containing 3000 or 6000 ppm 2-methylaniline•HCl for 2 years. The incidence of subcutaneous fibromas in control, low- and high-dose male rats was 0/20, 28/50 and 27/49, respectively. The incidence of mammary gland fibroadenomas in control, low- and high-dose female rats was 6/20, 20/50 and

35/49, respectively. The incidence of carcinomas in the urinary bladder of control, low- and high-dose female rats was 0/20, 9/45 and 22/47, respectively. A number of other tumors, primarily malignant and involving the spleen and the abdominal and scrotal mesothelia, also occurred at higher incidences among treated groups than among controls. The transformed low and high doses for these rats are 150 and 300 mg 2-methylaniline•HCl/kg/day, assuming that a rat consumes a daily amount of food equal to 5% of its body weight.

In a more recent study, Hecht et al. (1982) reported increased incidences of skin fibromas, mammary fibroadenomas, spleen fibromas and peritoneal sarcomas in groups of 30 male F344 rats maintained for 73 weeks on diets containing 4000 ppm 2-methylaniline•HCl followed by 20 weeks of observation. The skin fibroma response gave the greatest increase in incidence: 25/30 treated vs. 1/27 control. Hecht et al. (1982) reported that the rats received dosages of 62 mg/rat/day. The average body weight of the rats in the study was ~0.454 kg; therefore, the dosage was 136.6 mg/kg/day. Multiplying by the ratio of length of exposure/length of experiment (73 weeks/93 weeks) results in an expanded dose of 107.2 mg/kg/day.

Similarly, Weisburger et al. (1978) demonstrated increased incidences of subcutaneous fibromas and fibrosarcomas in groups of 25 male Sprague-Dawley rats maintained at TWA dietary concentrations of 2-methylaniline•HCl of 4667 and 9337 ppm for 18 months followed by a 6-month observation period. Incidences of these tumors were 0/16, 18/111, 18/23 and 21/24 for the matched controls, pooled controls, low-dose group and high-dose group, respectively. The estimated transformed low and high doses for these rats are 175 and 350 mg 2-methylaniline•HCl/kg/day assuming that rats consume food equivalent to 5% of their body weight/day and multiplying by the length of exposure/length of experiment (18 months/24 months).

In addition, both NCI (1979) and Weisburger et al. (1978) demonstrated the carcinogenicity of 2-methylaniline•HCl in mice. In a study by the NCI (1979), male and female mice were maintained at dietary levels of 1000 or 3000 ppm; the transformed dosages are 130 and 390 mg/kg/day assuming that a mouse consumes a daily amount of food equal to 13% of its body weight. A statistically significant increased incidence of tumors was observed only for liver tumors in female mice. The incidence of hepatocellular carcinoma and adenoma among female mice was 0/20, 4/49 and 13/70 (p=0.007) in control, low- and high-dose groups, respectively.

In the study by Weisburger et al. (1978), male and female mice were maintained at TWA dietary levels of 9333 or 18,667 ppm for 18 months, followed by a 3-month observation period. Using a food factor of 0.13 and multiplying by 18 months/21 months results in dosages of 1040 and 2080 mg/kg/day. Increased incidences of hemangiosarcomas and hemangiomas of the abdominal viscera occurred in both male and female mice. The incidences in treated males, which were higher than those in treated females were 0/14, 5/99, 5/14 and 9/11 in the matched controls, pooled controls, low-dose group and high-dose group, respectively.

In a previous determination of the q_1^* for 2-methylaniline, U.S. EPA (1984a) used the study by Hecht et al. (1982) because the dose-response data from this study yielded a higher q_1^* than did the data from the NCI (1979) or the Weisburger et al. (1978) studies. The q_1^* for 2-methylaniline and the data used to derive it are presented in Table 8-1. The transformed and expanded dose of 107.2 mg/kg/day for 2-methylaniline•HCl was converted to an equivalent dose of 80 mg/kg/day 2-methylaniline by multiplying by the ratio of the molecular weight of 2-methylaniline to that of 2-methylaniline•HCl (107.2 mg/kg/day x 107.15/143.62 = 80 mg/kg/day). The unadjusted q_1^* of 3.18×10^{-2} $(mg/kg/day)^{-1}$ was derived using the multistage model.

TABLE 8-1

Cancer Data Sheet for
Derivation of q_1^* for 2-Methylaniline

Compound: 2-methylaniline•HCl

Reference: Hecht et al., 1982

Species, Strain, Sex: rat, F344, male

Body weight: 0.454 kg (measured)

Length of exposure (le) = 73 weeks

Length of experiment (Le) = 93 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: skin fibroma

Route, vehicle: oral, diet (4000 ppm 2-methylaniline•HCl)

Experimental Doses or Exposures of 2-Methylaniline•HCl	Transformed Dose of 2-Methylaniline (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	1/27
62 mg/rat/day	80	25/30

(62 mg/rat/day ÷ 0.454 kg x 73 weeks/93 weeks x 107.15/143.62)

Unadjusted q_1^* from study = 3.2×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 2.4×10^{-1} $(mg/kg/day)^{-1}$

The human q_1^* of 2.4×10^{-1} $(mg/kg/day)^{-1}$ was calculated by multiplying the unadjusted q_1^* by the cube root of the reference human body weight (70 kg) to the weight of the rats in the study (0.454 kg) and by the cube of the ratio of the lifespan of the rat (104 weeks) to the duration of the study (93 weeks). Using the q_1^* of 2.4×10^{-1} $(mg/kg/day)^{-1}$, the water concentrations of 2-methylaniline associated with increased lifetime risk at levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.5×10^{-3}, 1.5×10^{-4} and 1.5×10^{-5} mg/ℓ, respectively, assuming a 70 kg man consumes 2 ℓ of water/day.

An unadjusted q_1^* of 2.4×10^{-2} $(mg/kg/day)^{-1}$ for 2-methylaniline•HCl can be calculated by substituting the dose of 107.2 mg/kg/day of 2-methylaniline•HCl in the multistage model (Table 8-2). Multiplying the unadjusted q_1^* by the cube root of the body weight ratio and by the cube of the ratio of L/Le results in a human q_1^* of 1.8×10^{-1} $(mg/kg/day)^{-1}$ for 2-methylaniline•HCl. The concentrations of 2-methylaniline•HCl in water associated with increased lifetime risk at levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.9×10^{-3}, 1.9×10^{-4} and 1.9×10^{-5} mg/ℓ, respectively.

TABLE 8-2

Cancer Data Sheet for
Derivation of q_1^* for 2-Methylaniline•HCl

Compound: 2-methylaniline•HCl

Reference: Hecht et al., 1982

Species, Strain, Sex: rat, F344, male

Body weight: 0.454 kg (measured)

Length of exposure (le) = 73 weeks

Length of experiment (Le) = 93 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: skin fibroma

Route, vehicle: oral, diet (4000 ppm 2-methylaniline•HCl)

Experimental Doses or Exposures of 2-Methylaniline•HCl	Transformed Dose of 2-Methylaniline•HCl (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	1/27
62 mg/rat/day	107.2	25/30

(62 mg/rat/day ÷ 0.454 kg x 73 weeks/93 weeks)

Unadjusted q_1^* from study = 2.4×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 1.8×10^{-1} $(mg/kg/day)^{-1}$

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The three chronic studies on 2-methylaniline•HCl (NCI, 1979; Weisburger et al., 1978; Hecht et al., 1982) are primarily concerned with the carcinogenic effects of 2-methylaniline•HCl and, therefore, provide little information on systemic toxicity. The NCI (1979) bioassay, however, indicates that chronic exposure to dietary 2-methylaniline•HCl at 3000 and 6000 ppm for rats, and at 1000 and 3000 ppm for mice, resulted in decreased mean terminal body weights in rats and mice, respectively (Table 9-1). Although a dose-related increase in mortality rate was observed in the rats ingesting 2-methylaniline•HCl, the increased incidence of tumors suggests that the decreased survival rate may have been a result of tumor development and, therefore, not an appropriate endpoint for the derivation of an RQ. As summarized in Table 9-1, the nonneoplastic lesions that occurred in rats ingesting 3000 or 6000 ppm of 2-methylaniline•HCl included splenic fibrosis and urinary bladder hyperplasia in both males and females and myocardial fibrosis in males only at 3000 ppm. Liver necrosis was observed in male and female rats ingesting 6000 ppm, but not 3000 ppm of 2-methylaniline•HCl. Because splenic fibrosis and urinary bladder hyperplasia are apparently preneoplastic changes, they were not included in the toxicity summary.

Strombeck (1946) and Ekman and Strombeck (1947) reported that rats receiving diets supplying 2-methylaniline at dosages of 15-24 mg/rat for 64 days followed by 7.5-12 mg/rat/day died by day 91 and had mucous membrane metaplasia and epithelial hyperplasia in the urinary bladder. Similar bladder lesions occurred in rats maintained on diets containing 0.1% (1000 ppm) 2-methylaniline for up to 341 days (Ekman and Strombeck, 1949). Since the bladder lesions in these studies were probably preneoplastic, they also are not included in the summary.

TABLE 9-1

Toxicity Summary for 2-Methylaniline·HCl (>99% pure) Administered in the Diet[a]

Species/ STrain	Sex	No. at Start	Average Weight (kg)	Exposure for 2 Years (ppm)	Transformed Animal Dose[b] (mg/kg/day)	Equivalent Human Dose[c] (mg/kg/day)	Response
Mouse/ B6C3F1	M	50	0.043	1000	130	11	reduced body weight gain
	F	50	0.035	1000	130	10	reduced body weight gain
Rat/F-344	M	50	0.375	3000	150	26	reduced body weight gain myocardial fibrosis
	F	50	0.225	3000	150	22	reduced body weight gain
Rat/F-344	M	50	0.33	6000	300	50	liver necrosis
	F	50	0.20	6000	300	43	liver necrosis

[a]Source: NCI, 1979

[b]The transformed dose was obtained by multiplying the dietary exposure in ppm by the food factor (0.13% for mice; 0.05% for rats). The food factor assumes that mice consume food the equivalent of 13% of their body weight as food each day and that rats consume food the equivalent of 5% of their body weight each day.

[c]Equivalent human dose calculated by multiplying the animal transformed dose by the cube root of the animal body weight to the reference human body weight.

Data used to calculate the CSs are presented in Table 9-2. Liver necrosis and myocardial fibrosis are effects that warrant an RV_e of 6. The lowest equivalent human dose at which either of these affects occurred is 26 mg/kg/day (low-dose male rats), which when multiplied by 70 kg yields an MED of 1820 mg/day. The MED corresponds to an RV_d of 1, which when multiplied by the RV_e of 6 yields a CS of 6 and an RQ of 1000 pounds.

The lowest equivalent human dose at which reduced mean body weight gain occurred was 10 mg/kg/day (female mice at 1000 ppm). Multiplying by 70 kg yields an MED of 700 mg/kg, which corresponds to an RV_d of 1.2. The RV_e is 4, which when multiplied by the RV_d yields a CS of 4.8, corresponding to an RQ of 5000 pounds.

Since the data for myocardial fibrosis yields the higher CS, these data are recommended as the basis for the RQ for 2-methylaniline•HCl (Table 9-3).

These data can also be used for the RQ for 2-methylaniline. Multiplying the MED of 1820 mg/day for myocardial fibrosis by the ratio of the molecular weights of 2-methylaniline to 2-methylaniline•HCl (107.15/143.62) yields an MED for 2-methylaniline of 1358 mg/day, which also corresponds to an RV_d of 1. Thus, the CS is 6 and the RQ is 1000 pounds.

Similarly, the MED of 700 mg/kg 2-methylaniline•HCl for reduced body weight gain is equivalent to an MED of 522 mg/day 2-methylaniline, which corresponds to an RV_d of 1.4. Multiplying the RV_d by the RV_e of 4 results in a CS of 5.6, which corresponds to an RQ of 1000 pounds.

Therefore, the data for myocardial fibrosis, resulting in a CS of 6 is recommended as the basis for the RQ for 2-methylaniline (Table 9-4).

TABLE 9-2

Oral Composite Scores for 2-Methylaniline•HCl*

Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ (lbs)
Mouse	130	700	1.2	reduced terminal body weight	4	4.8	5000
Rat	150	1820	1	myocardial fibrosis	6	6	1000

*Source: NCI, 1979

TABLE 9-3

2-Methylaniline•HCl
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	1820 mg/day
Effect:	myocardial fibrosis
Reference:	NCI, 1979
RV_d:	1
RV_e:	6
Composite Score:	6
RQ:	1000

*Equivalent human dose

TABLE 9-4

2-Methylaniline[a]
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose[b]:	1358 mg/day
Effect:	myocardial fibrosis
Reference:	NCI, 1979
RV_d:	1
RV_e:	6
Composite Score:	6
RQ:	1000

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[a]The compound administered was 2-methylaniline•HCl

[b]Equivalent human dose

A previous determination of the RQ for 2-methylaniline (U.S. EPA, 1985) used the data for reduced body weight gain of mice in the NCI (1979) study as the basis for the RQ of 1000 for 2-methylaniline. Apparently, the nonneoplastic lesions were not evaluated in that determination.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

According to IARC (1982a,b) and U.S. EPA (1984b), there is sufficient evidence for the carcinogenicity of 2-methylaniline•HCl in experimental animals (both rats and mice) and, although suggestive, inadequate evidence for the carcinogenicity of 2-methylaniline (bladder cancer) in humans. The evidence for the carcinogenicity of 2-methylaniline and 2-methylaniline•HCl in animals, which was discussed in detail in Section 5.1., is based on the increased incidence of splenic sarcomas, fibromas, angiosarcomas and osteosarcomas, subcutaneous fibromas, mammary fibromas and fibroadenomas and urinary bladder carcinomas and papillomas in rats fed 2-methylaniline•HCl (NCI, 1979; Weisburger et al., 1978; Hecht et al., 1982) and on the increased incidence of hemangiosarcomas and hepatocellular carcinomas and adenomas in mice fed 2-methylaniline•HCl (NCI 1979; Weisburger et al., 1978). The limited evidence for the carcinogenicity of 2-methylaniline and 2-methylaniline•HCl in humans is based on the increased incidence of bladder cancer observed in workers in the dye stuff industry (Case and Pearson, 1954; Case et al., 1954; Oettel, 1959, 1967; Oettel et al., 1968; Khlebnikova et al., 1970; Uebelin and Pletscher, 1954; Gropp, 1958; Vigliani and Barsotti, 1961; Zavon et al., 1973; Lipkin, 1972; Genin et al., 1978; Rubino et al., 1982). Workers were concurrently exposed to other potential bladder carcinogens such as benzidine, aniline and 2-naphthylamine. Further details were described in Section 5.1.

As discussed in Chapter 8, the data from the Hecht et al. (1982) study are the most appropriate for deriving the q_1*s, and hence the F factors, for 2-methylaniline•HCl and 2-methylaniline (Tables 9-5 and 9-6). The transformed dose of 107.2 mg/kg/day for 2-methylaniline•HCl was calculated by dividing the dose of 62 mg/rat/day as reported by Hecht et al. (1982) by the average body weight (0.454 kg) of the rats in the study and by multiplying by the ratio of duration of the treatment to the duration of the study (73 weeks/93 weeks). The transformed dose of 80 mg/kg/day for 2-methylaniline was calculated by multiplying the transformed dose of 107.2 mg/kg/day for 2-methylaniline•HCl by the ratio of the molecular weights of 2-methylaniline to 2-methylaniline•HCl (107.15/143.62). The unadjusted $1/ED_{10}$s, calculated using the multistage model, are 0.16 $(mg/kg/day)^{-1}$ for 2-methylaniline•HCl and 0.21 $(mg/kg/day)^{-1}$ for 2-methylaniline. The F factors, calculated by multiplying the $1/ED_{10}$ by the cube root of the ratio of the human body weight to the rat weight and by the cube of the ratio of the lifespan to the duration of the study, are 1.2 $(mg/kg/day)^{-1}$ for 2-methylaniline•HCl and 1.6 $(mg/kg/day)^{-1}$ for 2-methylaniline.

Because there is sufficient evidence that these chemicals are carcinogenic in animals, and suggestive, although inadequate, evidence that they are carcinogenic in humans, they are classified as IARC Group 2B (IARC, 1982b; U.S. EPA, 1984b) and EPA Group B2 (U.S. EPA, 1986b) chemicals; that is, they are probable human carcinogens. Chemicals that are placed in Potency Group 2 and EPA Group B2 have a LOW hazard ranking under CERCLA.

TABLE 9-5

Derivation of Potency Factor (F)
for 2-Methylaniline•HCl

Reference:	Hecht et al., 1982	
Exposure route:	oral	
Species:	rat	
Strain:	F344	
Sex:	male	
Vehicle or physical state:	diet	
Body weight:	0.454 kg	
Duration of treatment:	73 weeks	
Duration of study:	93 weeks	
Lifespan of animal:	104 weeks	
Target organ:	skin	
Tumor type:	fibroma	
Experimental doses/exposure:	0	62 mg/rat/day
Transformed doses:	0	107.2 mg/kg/day
Tumor incidence:	1/27	25/30
Unadjusted $1/ED_{10}$:	0.1552964 $(mg/kg/day)^{-1}$	
Adjusted $1/ED_{10}$ (F factor):	1.2 $(mg/kg/day)^{-1}$	

TABLE 9-6

Derivation of Potency Factor (F) for 2-Methylaniline*

Reference:	Hecht et al., 1982
Exposure route:	oral
Species:	rat
Strain:	F344
Sex:	male
Vehicle or physical state:	diet
Body weight:	0.454 kg
Duration of treatment:	73 weeks
Duration of study:	93 weeks
Lifespan of animal:	104 weeks
Target organ:	skin
Tumor type:	fibroma
Experimental doses/exposure:	0, 46.25 mg 2-methylaniline/rat/day (62 mg 2-methylaniline•HCl/rat/day x 107.2/143.7)
Transformed doses:	0 80 mg 2-methylaniline/kg/day
Tumor incidence:	1/27 25/30
Unadjusted $1/ED_{10}$:	0.2080975 $(mg/kg/day)^{-1}$
Adjusted $1/ED_{10}$ (F factor):	1.6 $(mg/kg/day)^{-1}$

*The compound administered was 2-methylaniline•HCl

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

Jaber, H.M., W.R. Mabey, S.T. Liu, T.W. Chow and H.L. Johnson. 1984. Data aquisition for environmental transport and fate screening for compounds of interest in the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

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USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984, USITC Publ. 1745, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, the following document was consulted during preparation of this HEEP:

U.S. EPA. 1984. Chemical Hazard Information Profile. Draft Report. ortho-Toluidine, ortho-Toluidine Hyphochloride. Office of Toxic Substances, U.S. EPA, Washington, DC. February 23, 1984.